



D6.6 – Study 2 initiation package

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Abstract	Study 2 Initiation Package describes in detail the framework for launching a prospective, mixed-methods feasibility study aimed at preventing and managing childhood and adolescent obesity across 6 countries in Europe. The document is used as a central resource for all participating pilot sites and stakeholders, detailing the essential procedures, data management strategies, governance structures, and ethical safeguards necessary for the study’s execution.
Keywords	digital health intervention, micro-moments, mixed-methods study, multicenter clinical trial, lifestyle modification, bio-sampling

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Nature of the deliverable:	<p>D6.6 Study initiation package for evaluating the impact of a personalized recommendation system for obesity prevention through citizen empowerment and engagement.</p> <p>Title of the study: Feasibility Study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Approach</p>

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EXECUTIVE SUMMARY

The BIO-STREAMS D6.6 Study 2 Initiation Package, represents an operational and technical guide for launching and managing the BIO-STREAMS prospective intervention study on childhood and adolescent obesity prevention. It is designed as living document that enables harmonized, ethical, and efficient execution of the BIO-STREAMS intervention study. It ensures that all operational, technical, and regulatory requirements are met, supporting high-quality data generation and participant safety across all European pilot sites. To this end the document describes:

A Centralized Reference Framework: The document describes all essential information required to initiate the intervention study, including detailed study protocols, recruitment strategies, regulatory and ethical compliance procedures, and operational management plans.

Governance and Oversight Structures: The deliverable defines clear roles and responsibilities for clinical and technical partners, outlines the multi-tiered governance and monitoring framework, and details the mechanisms for continuous risk management and participant safety oversight.

Data Management and Security Protocols: It describes the technical and organizational measures for secure, GDPR-compliant data collection, storage, harmonization, and sharing. The document describes the federated biobank infrastructure, pseudonymization policies, and the use of advanced IT systems—including the BIO-STREAMS Node Bundle and Information Management System—to safeguard sensitive participant data.

Technological Integration: The document outlines how digital tools, such as the ActiveHealth mobile application, serious games, micro-moment notifications, and AI-driven risk assessment module, are integrated into the study workflow.

Regulatory and Ethical Documentation: It includes templates and procedures for informed consent, privacy notices, and data subject rights, tailored for pediatric and adolescent populations. With this the document ensures all activities are aligned with Good Clinical Practice (GCP) and relevant national and EU regulations.

Operational Planning: The initiation package presents a detailed timeline, milestones, and key performance indicators for study execution, as well as appendices with supporting documents such as recruitment materials, questionnaires, and data collection instruments.

Continuous Quality and Risk Management: The document outlines the proactive and responsive monitoring framework, which includes, adverse event reporting, data quality checks, and regular review cycles by ethics and oversight committees.

Table of contents

Abbreviations	11
1 Introduction	13
1.1 Scope of Project	13
1.2 Scope of Report	16
2 Study Overview	18
3 Study Information	25
3.1 Background	25
3.2 Study Objectives	25
3.3 Intervention	26
3.4 Study and Execution Plan	27
3.4.1 Overall study execution	27
3.4.2 Intervention Timeline (participant level design)	28
4 Recruitment Strategy	30
5 Regulatory and Ethical Considerations	32
5.1 Ethics Approvals	32
5.2 Informed Consent	33
5.3 Data Oversight	33
5.3.1 Types of Personal Data	33
5.3.2 Lawful basis	34
5.3.3 Responsibility for processing	34
5.3.4 Data subject rights	34
5.3.5 Technical and Organizational Measures	35
5.3.6 Pseudonymization	35
5.3.7 Personal Data Sharing in Consortium	35
5.3.8 Personal Data Sharing Outside Consortium	36
5.3.9 Personal Data Retention	36
5.4 Continued Monitoring and Risk Management	36
5.4.1 Continuous Monitoring Procedures	42
5.4.2 Risk Management Strategy	42
5.4.3 Governance and Oversight	43
Conclusions	44
6 Appendix A: Detailed Study Protocol	45
6.1.1 Document History	46
6.1.2 Table of Contents	47
6.1.3 Executive Summary	51
6.2 General Information	56

6.2.1	Study Rationale.....	56
6.2.2	Current Knowledge and Background	58
6.2.3	Research Questions & Hypothesis	62
6.2.4	Primary and Secondary Aims and Outcomes	63
6.3	Study Design	64
6.3.1	Sample Size Justification	65
6.3.2	Study Population	67
6.3.3	Timing of the Study Procedures.....	71
6.3.4	Description of Study Procedures	73
6.3.5	Data Analysis	82
6.4	BIO-STREAMS Technological Components.....	85
6.4.1	BIO-STREAMS Federated Biobank: A Collection of Node Bundles.....	86
6.4.2	BIO-STREAMS Information Management System	86
6.4.3	BIO-STREAMS Dashboard.....	87
6.4.4	BIO-STREAMS ActiveHealth App.....	88
6.4.5	BIO-STREAMS Serious Games Suite	89
6.4.6	BIO-STREAMS Risk Assessment and Recommendation Engine	89
6.4.7	BIO-STREAMS Micro-moments	90
6.5	Data Flow, Data Operations and Data Procedures	91
6.5.1	Data Oversight	91
6.5.2	Categories of Personal Data	92
6.5.3	Legal Basis.....	92
6.5.4	Data Collection	93
6.5.5	Data Sharing and Responsibility of Processing	93
6.5.6	Data Subjects’ Rights	95
6.5.7	Data Storage	95
6.5.8	Data Harmonization & Data Curation.....	95
6.5.9	Data Retention	97
6.5.10	Security Measures	97
6.6	Study Quality Control Procedures.....	98
6.6.1	Study Deviation and Changes	98
6.6.2	Methodological Guidelines and Standards	98
6.6.3	Data Review and Processing	99
6.6.4	Study Suspension or Early Termination.....	99
6.6.5	Study Close-out.....	100
6.6.6	Data Reporting and Publication	100
6.6.7	Adverse Effects Monitoring and Reporting	100
6.7	Pilot Sites	101
6.8	Data Processors for the Intervention Study	104
6.9	Study financing.....	108

6.10	Appendices	109
6.10.1	Co-creation Workshop Materials.....	110
	Appendix 1: Child Persona Description.....	110
	Appendix 2: Questions for Input on Child Persona	112
	Appendix 3: Questions for Input on User Requirements, Study Design and Intervention	112
	Appendix 4: BIO-STREAMS ActiveHealth App Mock-ups	115
	Appendix 5: Serious Games mock-ups	119
	Appendix 6: Consent form Package for Co-creation Workshops.....	120
6.11	Intervention Study Materials	131
	Appendix 7: Consent form Package for the Intervention Study	131
7	Appendix B: Recruitment Strategy.....	144
7.1	Recruitment Strategy	144
7.1.1	Phase 1: Building a List of Interested Participants/Families	144
7.1.2	Phase 2: Initial Screening of Families.....	146
7.1.3	Phase 3: Formal Enrollment	146
7.1.4	Special Considerations	146
8	Appendix C: Standard Operating Procedures for the Prospective Study	148
8.1	GENERAL INFORMATION.....	151
8.1.1	Purpose of the Protocol.....	151
8.1.2	Scope of the Protocol.....	151
8.2	Roles and Responsibilities	152
8.3	REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE CLINICAL COORDINATOR	154
8.3.1	“Serious adverse event”	154
8.3.2	Severity assessment.....	155
8.3.3	Timelines	156
8.3.4	Immediate reporting and follow-up report	156
8.3.5	Non-immediate reporting.....	156
8.3.6	Start and end of reporting serious adverse events to the sponsor	156
8.3.7	Determining causality.....	156
2.5	Foreseen workflow of reporting of adverse events	159
8.4	REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE BIO-STREAMS SOP COMMITTEE.....	160
8.5	REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE INVESTIGATORS	160
8.5.1	“Adverse reactions”	160
8.6	ADVERSE EVENTS REPORTING IN VARIOUS STUDY PHASES AND MODES	160
8.6.1	Recruitment.....	160
8.6.2	Study execution.....	161
	Appendix.....	161
	Adverse Events Report Form	161

9 Appendix D: Self-report Outcome Measures164

List of figures

Figure 1: A visual representation of BIO-STREAMS Ecosystem 14

Figure 2: Process of collecting, storing, analyzing, and sharing Project data..... 16

Figure 3: Prospective Study Overall Timeline, *M refers to the month of the project and not the study.
27

Figure 4: Prospective Study Timeline of the intervention 28

Figure 5: Intervention study data collection timeline 75

Figure 6: BIO-STREAMS technological components..... 85

Figure 7: Child Persona Description..... 112

Figure 8: BIO-STREAMS ActiveHealth App mock-ups 118

Figure 9: Let’s move, Food quiz, and Fruit ninja mock-ups 119

Figure 10: Recruitment Leaflet Designed for The Study, Part 1. 145

Figure 11: Recruitment Leaflet Designed for The Study, Part 2. 146

List of tables

Table 1: BIO-STREAMS backbone services and packages	15
Table 2: Ethics Committee Approvals for BIO-STREAMS Project's Prospective Study	32
Table 3: Key Risks Requiring Continued Ethical Monitoring in BIO-STREAMS Study.....	37
Table 1: Subject distribution per cohort and pilot site (intervention study).....	66
Table 2: Subject distribution per cohort and piloting country (co-creation workshops).....	67
Table 3: The IDF definition of metabolic parameters in children and adolescents	70
Table 4 : A list of all collected measurements in the Intervention Study.....	78
Table 5: Detailed overview of self-report questionnaires, number of items, and time points of collection 79	
Table 6: Summary of targeted initial analyses	82

Abbreviations

AI	Artificial Intelligence
API	Application Programming Interface
BNB	BIO-STREAMS Node Bundle
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CHUL	Centre Hospitalier Universitaire de Liège
COMA	Children with Overweight/Obesity with Metabolic Abnormalities
CONM	Children with Overweight/Obesity with Normal Metabolic Parameters
CWO	Children Without Overweight/Obesity
DPA	Data Processing Agreement
DPO	Data Protection Officer
DTA	Data Transfer Agreement
EEA	European Economic Area
EQF	European Qualifications Framework
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reusable (data principles)
FPG	Fasting Plasma Glucose
GA	Grant Agreement
GDPR	General Data Protection Regulation
GCP	Good Clinical Practice
HCI	Human-Computer Interaction
HDL-C	High-Density Lipoprotein Cholesterol
IMS	Information Management System
IP	Internet Protocol
JCAs	Joint Controllership Agreements
KPI	Key Performance Indicator
LOINC	Logical Observation Identifiers Names and Codes
ML	Machine Learning
NGO	Non-governmental Organization
OMOP	Observational Medical Outcomes Partnership (Common Data Model)

SAF	Security Assurance Framework
SD	Standard Deviation
SDG	Synthetic Data Generator
SNP	Single Nucleotide Polymorphism
TCP	Transmission Control Protocol
T2DM	Type 2 Diabètes Mellitus
WHO	World Health Organization
WP	Work Package
z-score	Standard Score (statistical measure)

1 Introduction

BIO-STREAMS, here referred to as the '**Project**,' is a multi-disciplinary EU project, primarily focusing on addressing childhood and adolescent obesity. The Project's objectives, components, and deliverables are manifold. To begin with, it aims to develop and implement three key elements:

- EU-wide Childhood/Adolescence Obesity Biobank, designed to facilitate data sharing across the EU for research and innovation purposes
- Accessible Obesity Platform, utilizing the resources of the Biobank to offer various services, including applications
- EU Community Network dedicated to Childhood/Adolescence Obesity

The Project spans across four years, from May 2023 (M1) to April 2027 (M48).

Childhood obesity is a pressing public health issue that poses serious health risks to millions of children and adolescents across Europe and globally. The complex etiology of obesity, involving interplay between genetic, environmental, and lifestyle factors, requires multifaceted interventions. In response to this challenge, the BIO-STREAMS project was initiated to develop a digital platform designed to support the prevention and management of obesity among young populations. This platform aims to integrate the latest research and evidence-based practices into tools that are both practical and accessible for healthcare providers, educators, policymakers, and families.

This document describes and defines the Study Initiation Package for the retrospective study "Using electronic health records and AI to improve health outcomes for children with obesity across Europe" (ISRCTN12357025) which provides a comprehensive framework for launching and managing the research. It serves as a central resource for all pilot sites, encompassing essential information, such as the study's objectives, design, and methodology, as well as strategies for participant recruitment, ensuring regulatory compliance, and outlining operational management.

1.1 Scope of Project

The scope of the Project's is detailed within the GA and Horizon Europe Proposal ('**Proposal**').¹ This section offers a concise overview, emphasizing the Project's most pertinent aspects for this Report.

As mentioned earlier, BIO-STREAMS is a diverse project aimed at addressing childhood and adolescent obesity through the utilization of data and technology. The Proposal includes a visual representation of the BIO-STREAMS 'Ecosystem,' summarizing its various elements (Figure 1).²

¹ Proposal for Horizon Europe Work Programme 2021 – 2022 / Health HORIZON-HLTH-2022-STAYHLTH-01-05-two-stage - Prevention of obesity throughout the life course Multi-Pillar Framework for children Anti-Obesity Behaviour building on an EU Biobank, Micro-Moments and Mobile Recommendation Systems. Ref. Ares (2022) 6184745 - 07/09/2022.

² Proposal, 7.

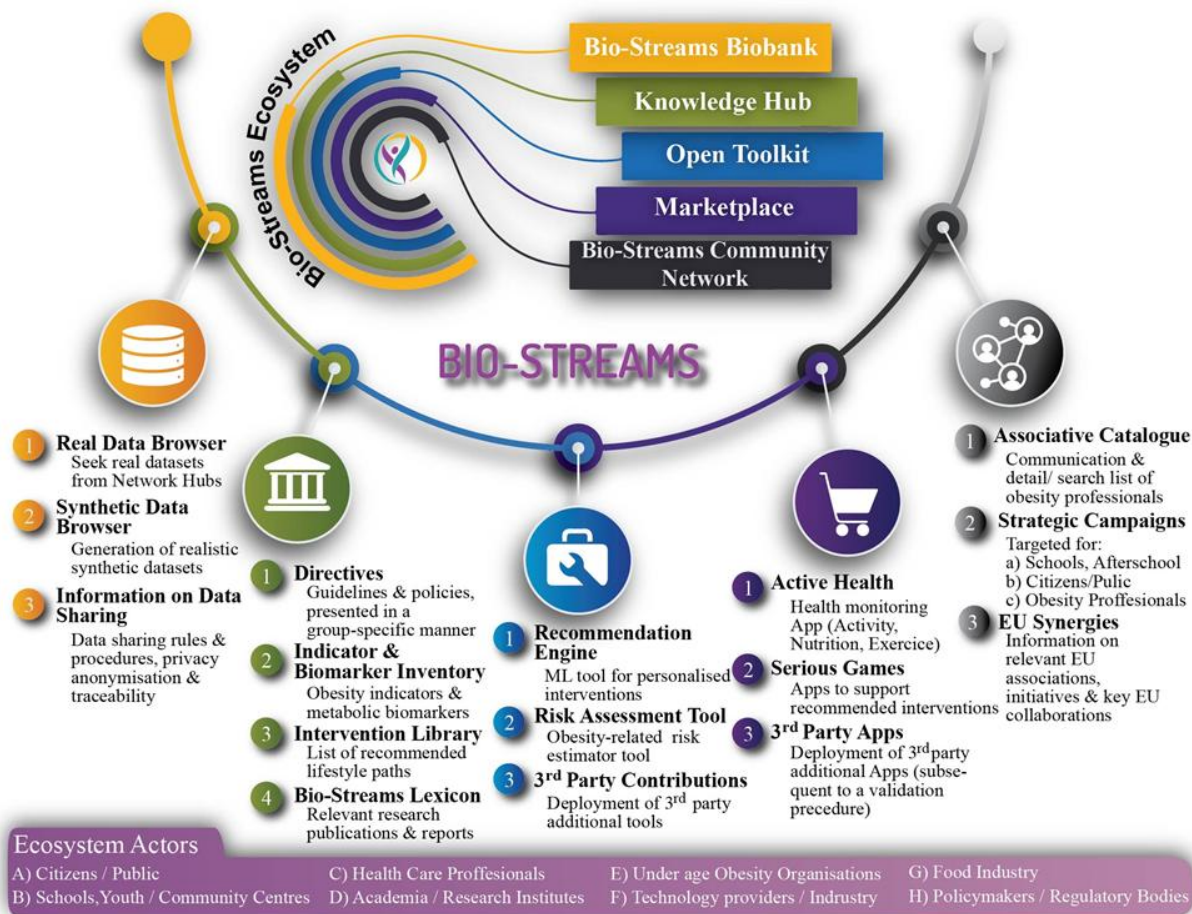


Figure 1: A visual representation of BIO-STREAMS Ecosystem

The BIO-STREAMS ‘Ecosystem’ incorporates five main components, supported by the necessary backbone services & packages’,³ which are presented in Table 1:⁴

³ Proposal, 6.

⁴ Proposal, 7.

Table 1: *BIO-STREAMS backbone services and packages*

Service/Package	Short Description
<i>Bio-Streams Node Bundle (BNB)</i>	It includes hardware & software resources, installed at every <i>Bio-Streams</i> member site to create a Data Hub. All Hubs formulate a Hub Network constituting the <i>Bio-Streams</i> Biobank.
<i>Synthetic Data Generator (SDG)</i>	Service for on-demand creation of synthetic datasets based on knowledge extracted from real data in the <i>Bio-Streams</i> Biobank.
<i>Data Handler</i>	Service for dataset cataloguing, browsing, requesting, sharing & tracking. Operation will be governed by the <i>Bio-Streams</i> regulatory framework and Data Management Plan.
<i>Security Assurance Framework (SAF)</i>	SAF will ensure secure and privacy-preserving operation of all <i>Bio-Streams</i> components and services, dynamically operating both synchronously and asynchronously.
<i>ML tools</i>	Federated ML supporting knowledge representation & extraction (e.g. SDG), risk assessment and pathway recommendation.

Structurally, the Project is organized into five ‘Phases’, which are summarized from the Proposal⁵ as follows:

1. Build knowledge foundation for the design, development and implementation of BIO-STREAMS
2. Build BIO-STREAMS Biobank
3. Integrate BIO-STREAMS Solution
4. Create BIO-STREAMS Community Network
5. Validate and Evaluate the BIO-STREAMS Solution in multiple Pilot-Sites,

While each Phase holds significance for the Project's overarching goals, the Biobank stands as a cornerstone, essential for advancing other Phases or components within the BIO-STREAMS Ecosystem. The Project entails gathering and examination of biological samples. However, it is the digitized data that will primarily drive the Project toward its objectives, encompassing metadata extracted from biological material.⁶ Therefore, the BIO-STREAMS Biobank is best conceptualized as a virtual biobank, serving as an 'EU-wide data-sharing centre'⁷ for childhood/adolescent obesity, housing various data types such as demographic, behavioral, clinical, genetic/epigenetic, and cost data.⁸ The critical role of the BIO-STREAMS Biobank within the Project is depicted in Figure 2:⁹

⁵ Proposal, 7-18.

⁶ Proposal, 12. Note that the GDPR distinguishes biological material from data that is derived from it (at recital 33).

⁷ Proposal, 2.

⁸ Ibid.

⁹ Proposal, 12.

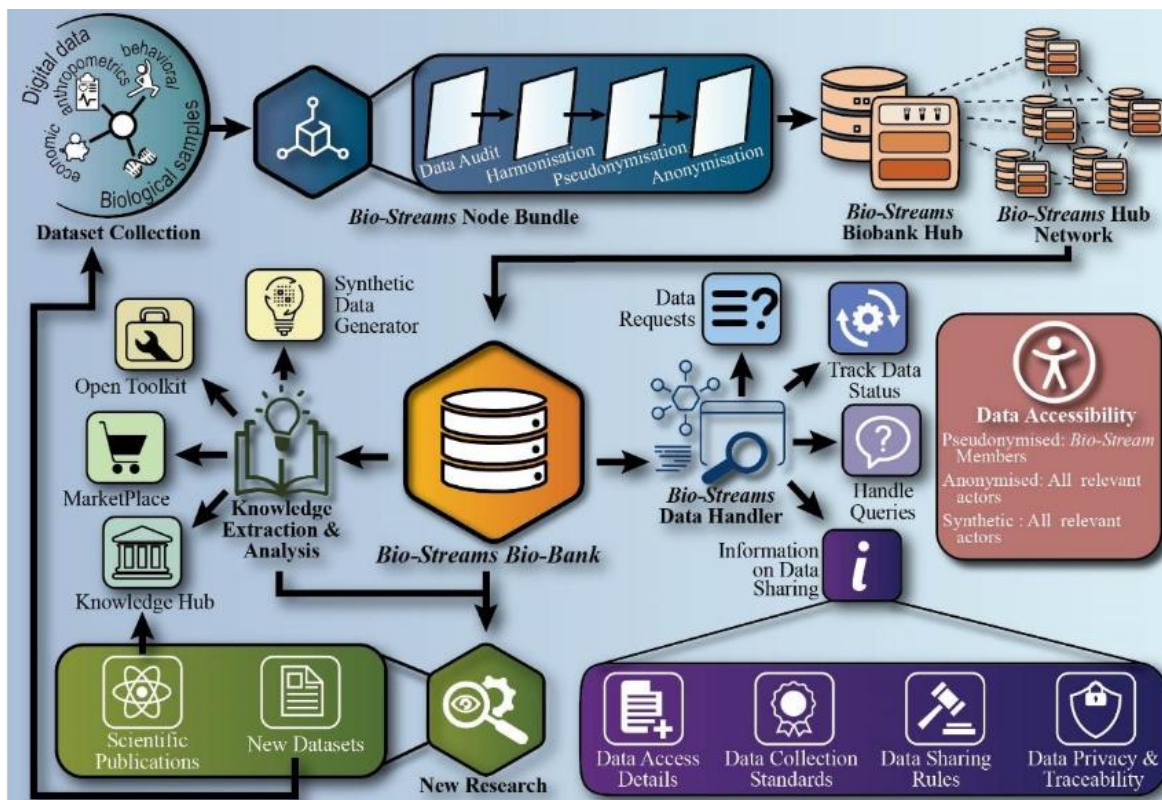


Figure 2: Process of collecting, storing, analyzing, and sharing Project data

Figure 2 illustrates the process of collecting, storing, analyzing, and sharing Project data in connection with the BIO-STREAMS Biobank.

1.2 Scope of Report

The Study Initiation Package (SIP) is designed to provide a complete overview and guide for initiating and conducting the Retrospective Study, titled “Feasibility study of a personalized recommendation system for obesity prevention: a mixed methods approach” (<https://doi.org/10.1186/ISRCTN46980>). It defines critical aspects necessary for the successful launch and management of the clinical study. The document serves as a central reference point for investigators, sponsors, regulatory bodies, and other stakeholders involved in the trial execution.

Key areas that this document includes are:

1. Study Overview: Provides a concise summary of the trial, including its objectives, design, and key endpoints
2. Scientific Background: Contextualizes the study within current medical and scientific knowledge
3. Detailed Study Design: Outlines the investigational plan, methodology, and specific procedures to be followed
4. Participant Recruitment: Presents a comprehensive strategy for identifying, engaging, and enrolling suitable study participants
5. Regulatory Compliance: Addresses ethical considerations and ensures alignment with Good Clinical Practice (GCP) guidelines and relevant regulatory requirements

6. **Operational Framework:** Delineates responsibilities, oversight mechanisms, and risk management strategies
7. **Study Management:** Includes timelines, milestones, and key performance indicators for monitoring study progress
8. **Essential Documentation:** Incorporates critical documents such as the full study protocol and other relevant documents and forms

2 Study Overview

Title	Feasibility Study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Approach
Scientific Title	BIO-STREAMS: A Multi-Center Mixed Method Trial Evaluating Personalized Digital Interventions for Prevention of Childhood and Adolescent Obesity Based on Genetic, Epigenetic, and Behavioral Factors
Aim	<p>Primary aims:</p> <ol style="list-style-type: none"> 1. To evaluate the impact of genetic predisposition and epigenetic modifications on efficacy of behavior modification. 2. To evaluate the acceptance and impact of BIO-STREAMS recommendation tools and micro-moment-based interventions for lifestyle modifications on awareness and engagement in preventive behaviors of children, adolescents, and families. <p>Secondary aims:</p> <ol style="list-style-type: none"> 1. To identify similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications differentiating between the three cohorts. 2. To empower parents and children to prevent obesity through new tools and services for informed decisions about lifestyle choices. 3. To evaluate the possible benefits of the recommendation tool towards health outcomes in children & adolescents. 4. To analyze the impact of personalized risk assessment on preventive behavior. 5. To quantify medical costs related to overweight/obesity management.
Registration of the Study	ISRCTN44876661
DOI:	https://doi.org/10.1186/ISRCTN44876661
Study design	Mixed methods study with a within subject design (3 arms, no randomization) in 7 piloting sites
Primary objective(s)	<p>The primary objectives of the BIO-STREAMS study are:</p> <ul style="list-style-type: none"> • To evaluate the impact of genetic predisposition and epigenetic modifications on the efficacy of behavior modification interventions for obesity prevention. • To evaluate the acceptance and impact of BIO-STREAMS recommendation tools and micro-moment-based interventions for lifestyle modifications on awareness and

engagement in preventive behaviors of children, adolescents, and families.

Secondary objective(s)	<p>The secondary objectives of the BIO-STREAMS study are:</p> <ul style="list-style-type: none"> • To identify similarities and differences in clinical presentation, personal exposome, genetic predisposition, and epigenetic modifications differentiating between the three cohorts: children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM), and children with overweight/obesity with metabolic abnormalities (COMA). • To empower parents and children to prevent obesity through new tools and services for informed decisions about lifestyle choices. • To evaluate the possible benefits of the recommendation tool towards health outcomes in children and adolescents by measuring improvements in health/food literacy, quality of life and well-being, increases in self-regulation, and decreases in mental distress (including anxiety, depression, and self-perceived stigma). • To analyze the impact of personalized risk assessment on preventive behavior (i.e., adherence to recommendations) of children and families. • To quantify medical costs related to overweight/obesity management.
Primary endpoints	<p>Number of new biological pathways conferring efficacy of preventive behavior.</p> <p>Acceptability and usability of the mobile application and interventions measured through: Affective attitude (user experience), Participant engagement, Trust and acceptance, Perceived burden of the behavior modifications, Adherence to the recommended interventions</p>
Secondary endpoint	<ol style="list-style-type: none"> (1) Sensitivity and specificity of defining the subsets of patients at risk for metabolic dysfunction. (2) Reduction in body weight of 5% or centiles of BMI by 5 percentile points or z-score BMI change by 0.25, reduction in bodyfat, reduction in other anthropometric parameters. (3) Improvement of health/food literacy (measured using the FNLIT questionnaire). (4) Improvement in quality of life (measured using the KIDSCREEN-10 assessment). (5) Improvement in well-being (measured using the WHO-5 Well-being Index). (6) Increase in self-regulation (measured using the SRQ for exercise dimension and SREBQ for eating behavior). (7) Decreased mental distress, including anxiety (measured using PSWQ-C), depression (measured using CES-D), and self-perceived stigma (measured using WSSQ). (8) Medical costs related to overweight/obesity management.

Duration of clinical investigation 25 months

Subject population

Three groups:

- Children without overweight/obesity (CWO)
- Children with overweight/obesity with normal metabolic parameters (CONM)
- Children with overweight/obesity with metabolic abnormalities (COMA)

In total 1,050 participants (350 per group) to be included across all the study's 7 clinical sites:

1. University Medical Centre Maribor (UKCM)
2. National and Kapodistrian University of Athens (NKUA)
3. Karolinska Institute (KI)
4. Blocks Health and Social Care EOOD (BLOCKS)
5. Hospital Universitari Vall d'Hebron (VHIR)
6. Centre Hospitalier Universitaire de Liège (CHUL)
7. Penteli General Childrens' Hospitasl (PENTELI)

Sex distribution: In 2020, around 175 million children and adolescents aged 5-19 years worldwide were considered obese¹⁰. In the study female and male subjects will be recruited in proportions. However, it must be noted that boys are more susceptible to obesity than girls. A significant difference between genders in European cohorts was in favor of girls, i.e. fewer girls were obese than boys. On average across 23 EU countries, 14% of boys and 10% of girls aged 7-8 years were obese, according to the COSI study¹¹. Overall, the prevalence of overweight and obesity among boys is 31%, while among girls it is 28%¹².

Sample size: calculated to support ANOVA repeated measures statistical test with within-between interaction (3 groups, 2 measurements). Anticipating a small effect size ($f = 0.05$), which is consistent with related behavioral intervention studies for obesity and using conventional significance threshold ($\alpha = 0.05$) and statistical power ($1-\beta = 0.80$), the analysis indicated that 969 participants would be needed to detect the anticipated effects (323 per group). To account for an expected 8-10% dropout rate, which is typical for longitudinal studies involving children and adolescents, the recruitment target was increased to 1,050 participants (350 per group).

This approach ensures the study is adequately powered to detect clinically meaningful changes, as research shows that even

¹⁰ <https://www.statista.com/statistics/1386146/number-of-obese-children-and-adolescents-worldwide-forecasts-by-gender/>

¹¹ https://www.oecd-ilibrary.org/sites/health_glance_eur-2018-26-en/index.html?itemId=/content/component/health_glance_eur-2018-26-en

¹² <https://www.who.int/europe/news/item/03-03-2023-childhood-obesity--five-facts-about-the-who-european-region>

	<p>modest interventions producing 5-10% reductions in weight can significantly improve health outcomes. The sample will be distributed across seven clinical sites in six European countries, with approximately 150 participants per site, ensuring representation across diverse cultural, socioeconomic, and healthcare contexts.</p>
Number of Sites	<p>7 clinical sites:</p> <ol style="list-style-type: none"> 1) UKCM 2) NKUA 3) KI 4) BLOCKS 5) VHIR 6) CHUL 7) PENTELI
Sponsor information	<p>University of Maribor (UM), Research organization</p> <p>University Medical Center Maribor (UKCM), Hospital/treatment Centre</p> <p>National and Kapodistrian University of Athens, Center for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence, Aghia Sophia Children’s Hospital (NKUA), Hospital/treatment Centre</p> <p>Karolinska Institute, Department of Biosciences and Nutrition (BioNut) (KI), Research organization</p> <p>Blocks Health and Social Care EOOD, Department of Physiotherapy and rehabilitation for children (BLOCKS), Hospital/treatment Centre</p> <p>Hospital Universitari Vall d’Hebron, Vall d’Hebron Institut de Recerca (VHIR), Hospital/treatment Centre</p> <p>Centre Hospitalier Universitaire de Liège, Department of Pediatrics (CHUL), Hospital/treatment Centre</p> <p>Penteli General Children’s Hospital, Penteli General Children’s Hospital (PENTELI), Hospital/treatment Centre</p>
External organizations involved in the clinical investigation	<p>No organizations external to the BIO-STREAMS consortium will be involved in clinical investigation. Each clinical site, contributing with data, will allocate a pilot leader (e.g. the Principal Investigators) to oversee the operations within the pilot study. Project’s Clinical Manager, Izidor Mlakar (University of Maribor) will oversee the execution of all the studies. Oversight of the Data Operations will be carried out by Magdalena Góralczyk, Peter Davis and Lucrezia Nicosia (White Label Consultancy APS) and the Project’s Data Protection Officer, Dimitris Kalogeras (ICCS). Each clinical partner also has their own DPO (contact details of each provided below).</p>

Inclusion criteria	Participant type(s): Healthy volunteer, Patient
	<p>Overall Criteria:</p> <ul style="list-style-type: none"> • ability to give informed consent • owning a smartphone or tablet (available in the home environment, not necessarily personal device of the participant) OR parent owning a smartphone (for younger children) age: 5-18 years • for age group of 5-12 years, parents will need to be involved together with the children <p>Inclusion into groups:</p> <ul style="list-style-type: none"> • Children with Overweight: BMI more than 1 SD to 2 SD above the median of the WHO growth reference for children adolescent • Children with Obesity: BMI more than 2 SD above the median of the WHO growth reference for children and adolescent • Children with Normal weight <p>Further, we will stratify the group with children with overweight or obesity into two groups based on IDF criteria:</p> <ul style="list-style-type: none"> • Children with overweight/obesity with normal metabolic parameters (CONM) • Children with overweight/obesity with metabolic abnormalities (COMA) <p>For children under 16, one criterion needs to be fulfilled to classify for COMA group, for children 16 and above, two criteria need to apply. The third, control group, will consist of children also recruited in a clinical setting, but with normal weight:</p> <ul style="list-style-type: none"> • Children without overweight/obesity: BMI up to 1 SD above the median of the WHO growth reference for children and adolescent
Exclusion criteria	<ul style="list-style-type: none"> • age under 5 or above 18 years old • severe mental disorder (schizophrenia, bipolar disorder, severe depressive disorder) • inability to give informed consent and/or assent (e.g., in case of intellectual disability), by parents or children (age depending on the local legislation) • severe cognitive disorder that would prevent to follow-up on recommendations, and epileptic • disorders: <ul style="list-style-type: none"> ➢ children with severe chronic medical conditions ➢ orthopedic affection limiting physical activity ➢ use of medication known to effect body weight ➢ known family issues that would affect general compliance and attendance at follow-up visits • diagnosis of clinical condition that requires a specific diet (e.g. coeliac disease, allergies,...)

- BMI lower than 2 SD below the median of the WHO growth reference for children and adolescents

Data Oversight

The study plans to process special categories of personal data (i.e. ‘sensitive data’) of children, which demands a strong emphasis on data oversight. To ensure compliance with ethical and legal obligations including the General Data Protection Regulation (GDPR), and to safeguard patient privacy, appropriate and state-of-the-art organizational and technical measures will be adopted. This includes the use of encryption technologies to ensure access to information about the study participants is limited to what is necessary to lawfully achieve the purposes of the study. All data processing will occur in the EU.

The data oversight measures include:

- Appropriate organizational and technical measures to ensure compliance with ethical and legal obligations including GDPR
- Encryption technologies limit access to participant information to what is necessary for the study purposes
- Data processing exclusively within the European Economic Area and Switzerland
- Clinical partners acting as data controllers, determining the purposes and means of processing
- Technical partners acting as data processors, operating under the authority of clinical partners
- Data Transfer Agreements (DTA), Data Processing Agreements (DPA), and Joint Controllership Agreements implemented as needed
- The BIO-STREAMS Node Bundle (BNB) ensuring a decentralized federated data management system where pseudonymized and standardized datasets are stored locally
- Only pseudonymized personal data available to BIO-STREAMS partners
- Clinical partners retaining the ability to directly identify participants from pseudonymized datasets
- Personal data stored indefinitely or until participants initiate their right to be forgotten or withdraw consent, with periodic reviews at least every 5 years

Clinical investigation financing

This Clinical study is part of the BIO-STREAMS European Project funded within the research and innovation program of the Horizon Europe under N° 101080718. The funding source had no impact on the decision to carry out the study or in its design. The funding source will have no impact on the decisions related to publishing this research or its outcomes. The content of this document does not reflect the official opinion of the European Union or any other institution.

Person compensation	paying	No compensation is provided for costs and time incurred in participating in a clinical investigation. The clinical sites will consider compensation for travel costs.
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3 Study Information

The details of the study are defined in Appendix A: Detailed Study Protocol. In this section we provide a brief overview of the study.

The BIO-STREAMS prospective study is a mixed methods feasibility study focused on childhood obesity prevention using personalized recommendation systems. The study is designed with two parts:

- The **Co-creation workshops**: These involve children aged 5-18 from, parents and experts from the six European countries involved to gather feedback on the study design, digital tools, and intervention strategies.
- The **Intervention study**: A 6-month prospective study with 1,050 participants (350 each from three cohorts) to validate digital solutions and assess their impact on health outcomes.

The study includes three cohorts: Children without overweight/obesity (CWO), Children with overweight/obesity with normal metabolic parameters (CONM), and Children with overweight/obesity with metabolic abnormalities (COMA). Children are aged 5-18 years and recruited across seven clinical sites in six European countries (Slovenia, Greece, Sweden, Bulgaria, Spain, Belgium).

The co-creation activities were carried out and are reported in D6.1, thus this deliverable and the initiation package will only focus on the implementation of the interventional study.

3.1 Background

Childhood obesity represents one of the most challenging public health problems of the 21st century, with epidemic proportions worldwide and significant associated morbidity and mortality. According to the World Health Organization (WHO), over 41 million children under age 5 and more than 340 million children and adolescents aged 5-19 are estimated to be overweight or obese globally. The etiology of obesity is multifaceted, involving complex interactions between genetic predisposition, epigenetic modifications, environmental factors, and lifestyle choices. Despite considerable evidence supporting the role of environmental factors such as sedentary lifestyle and high-calorie nutrition, there is also strong evidence for genetic components in common obesity. Recent progress in epigenetics has revealed the differential expression of multiple genes before and after obesity interventions, suggesting that transient environmental effects experienced early in life may lead to permanent epigenetic modifications.

The BIO-STREAMS project addresses these challenges by developing a Multi-Pillar Framework that builds on an EU biobank, micro-moments, and mobile recommendation systems to deliver personalized interventions for preventing and managing childhood obesity across multiple European settings.

3.2 Study Objectives

The BIO-STREAMS intervention study is designed to validate personalized digital solutions for childhood obesity prevention and management while investigating the biological and behavioural factors that influence intervention effectiveness. The study will recruit 1,050 participants (350 in each of three cohorts) across seven clinical sites in six European countries.

The study is driven by the following primary research question:

- (1) What impact will the personalized recommendation for lifestyle modification have on awareness and adherence to healthy behaviors of children, adolescents, and families?

The secondary research questions focus on identifying high-risk groups for metabolic dysfunction in obese children and adolescents, and exploring how genes and lifestyle modifications can influence treatment effectiveness and health outcomes. We identify three secondary research questions:

- (2) What are the similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications between patients with obesity (metabolically healthy and metabolically unhealthy) and healthy individuals (control), to define subsets (=clusters) of patients who are at the highest risk for metabolic dysfunction?
- (3) What is the impact of genetic predisposition and epigenetic modifications on efficacy of behavior modification (i.e. physical activity and micro-moments)?
- (4) Can the use of the EU Childhood Obesity Platform and the risk assessment modules contribute to health outcomes and well-being of children, and adolescents?

Primary outcomes include:

- (1) Number of new biological pathways conferring efficacy of preventive behavior.
- (2) Acceptability and usability of the mobile application and interventions measured through affective attitude (user experience) and participant engagement, trust and acceptance, perceived burden of the behavior modifications and adherence.

Secondary outcomes include:

- (1) Sensitivity and specificity of defining the subsets of patients at risk for metabolic dysfunction.
- (2) Reduction in body weight of 5% or centiles of BMI by 5 percentile points or z-score BMI change by 0,25, reduction in body fat, reduction in other anthropometric parameters.
- (3) Improvement of health/food literacy.
- (4) Improvement in quality of life.
- (5) Improvement in well-being.
- (6) Increase in self-regulation.
- (7) Decreased mental distress, including anxiety, depression, and self-perceived stigma.
- (8) Mapping of medical costs related to overweight/obesity management.

3.3 Intervention

The BIO-STREAMS intervention is a comprehensive, personalized digital approach to obesity prevention that extends over a 6-month period per participant. The intervention consists of several interconnected components:

ActiveHealth Mobile Application: A central digital tool providing personalized lifestyle recommendations tailored to specific goals, with flexibility to adjust objectives related to activities and nutrition. The app delivers personalized tips about healthy eating and physical activity, allows users to track progress, and integrates with caregivers' therapy protocols.

Serious Games Suite: Gamified exercises focusing on physical activity to increase intrinsic capacity and motivate users to adopt lifestyle recommendations. These games incorporate both experiential and vicarious learning approaches, with competitive avatars acting as life coaches during physical activity interventions.

Micro-moments: Brief, contextual digital interventions delivered at key decision points throughout the day. These push notifications provide timely recommendations based on the

user's profile, addressing four types of moments: "I-want-to-know," "I-want-to-go," "I-want-to-do," and "I-want-to-buy" moments.

Risk Assessment Tool: An AI-driven analytical component that provides personalized prediction of risk levels for adverse metabolic outcomes attributed to obesity and overweight, using ML-based modeling.

Recommendation Engine: A rule-based system delivering personalized programs of validated lifestyle recommendations for prevention and healthy living, based on content from the BIO-STREAMS Knowledge Hub.

3.4 Study and Execution Plan

3.4.1 Overall study execution

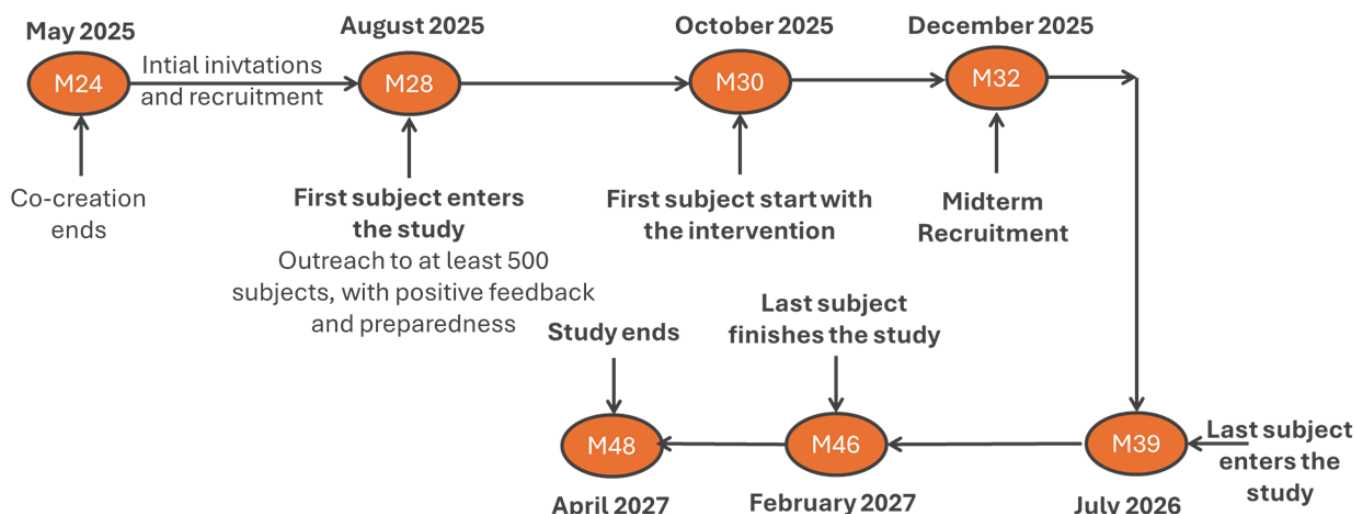


Figure 3: Prospective Study Overall Timeline, *M refers to the month of the project and not the study.

Figure 3 outlines the initial overall study execution plan with the following key activities (M refers to the month of the project and not the study):

1. May 2025 (M24):

- All the co-creation activities and patient-public-involvement activities have been carried out
- The study protocol is finalized and reflects the values and perspective of the real-world subjects representing participant Personas of the study.
- All sites have submitted the amendments to the relevant ethics committee

2. May 2025 (M24) to August 2025 (M28):

- All relevant DTA/DPAs are signed and come into force.
- The study had been presented to possible subjects, at least 500 subjects per pilot site
- At least 40 subjects per partner site have committed to participate
- All sites receive confirmation related to the amendments that were result of the co-creation activities and patient-public-involvement activities

1. August 2025 (M30) to February 2027 (M46):

- Execution of the study and progressive inclusion of participants, each participant starts with the study immediately after they are recruited
- Last participant enters the study in M39
- Last participant finishes with the study at M46

February 2027 (M46) to April 2027 (M48):

- Analysis of the results
- Presentation of the results to the subjects in form of workshops

3.4.2 Intervention Timeline (participant level design)

The timeline for the prospective study is presented in Figure 4.

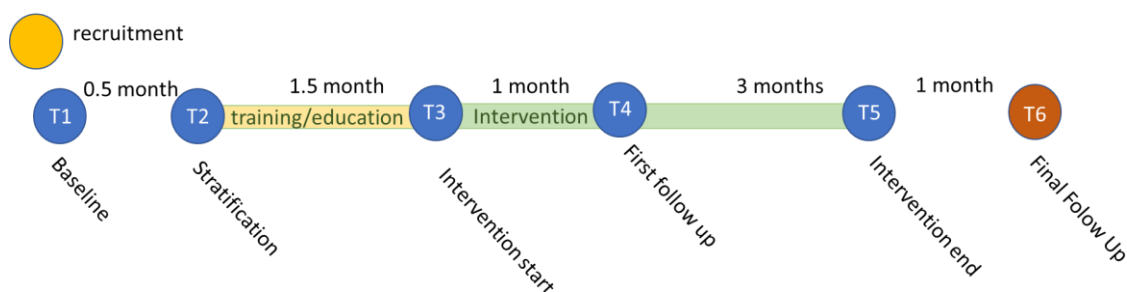


Figure 4: Prospective Study Timeline of the intervention

Baseline Assessment (2 Months)

- Collection of anthropometric measurements (height, weight, waist circumference)
- Saliva samples for genetic and epigenetic markers
- Baseline questionnaires on lifestyle, health literacy, and psychological factors (see questionnaires in Appendix D)
- Stratification into participant groups (CWO, CONM, COMA)
- Training and educational activities to familiarize participants with the digital tools

Supervised Active Intervention (1 Month)

- Participants use the BIO-STREAMS digital tools under clinical supervision
- Initial recommendations are generated by the recommendation engine and reviewed by clinicians
- Baseline data is fed to the risk assessment tool to provide information on overall risk
- Participants document their adherence to recommendations through the app

Unsupervised Active Intervention (3 Months)

- Participants continue using the digital tools independently
- Self-management recommendations continue based on individual progress
- Where necessary, interventions are adjusted to better fit individual contexts
- Individual consultations are available upon request or if low engagement is detected
- Questionnaires on lifestyle, health literacy, and psychological factor
- Measurement of adherence and participant engagement through the app

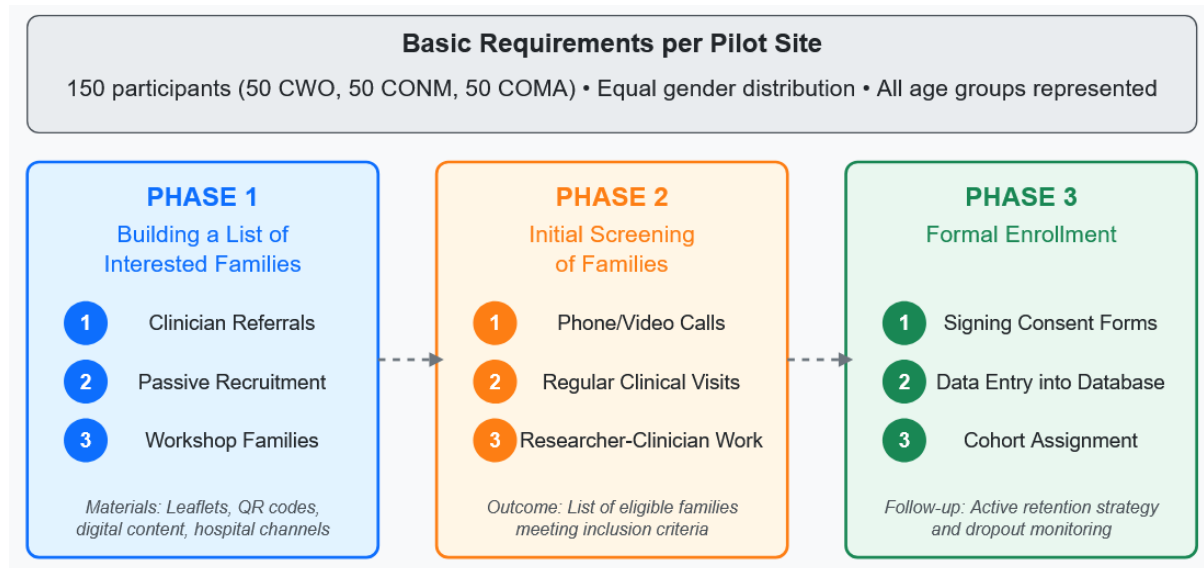
Follow up Assessment (1 Month after the intervention ends)

- Repeat collection of anthropometric measurements and saliva samples
- Final set of questionnaires on psychological measures, user experience, and health literacy
- Presentation of individual results to participants by clinicians
- Questionnaires on lifestyle, health literacy, and psychological factor

Throughout the intervention, participants receive standard care alongside the digital interventions. The ActiveHealth app and serious games provide ongoing support, encouragement, and education about healthy lifestyle choices, while the micro-moments approach delivers contextually relevant prompts to influence behavior at critical decision points.

4 Recruitment Strategy

In this section we outline the BIO-STREAMS recruitment strategy. The details of the strategy are presented in Appendix B: Recruitment Strategy. It is designed to ensure appropriate participant distribution across all study sites. Each pilot site is required to recruit 150 participants with equal distribution across the three cohorts (50 children without overweight/obesity, 50 children with overweight/obesity with normal metabolic parameters, and 50 children with overweight/obesity with metabolic abnormalities), while maintaining roughly equal representation across all age groups (5-18 years old) and genders.



In the BIO-STREAMS project we will explore and exploit the internal resources. Centers will conduct reviews of their clinical departments to identify clinicians with relevant expertise. The recruitment process will be carried out in three distinct phases. In Phase 1 that will end by August 2025, pilots will focus on building a list of interested participants and families through multiple channels. The primary strategy involves clinician referrals, where doctors identify and recommend families who have demonstrated responsiveness and engagement in previous healthcare interactions. Complementing this approach is passive recruitment through informational materials such as leaflets (see Appendix B: Recruitment Strategy) with QR codes distributed in clinics, digital content displayed on hospital screens, animations explaining the participant journey, and communications through internal hospital channels, magazines, and direct patient mailing lists and phone contact. Additionally, pilot sites may re-engage families who previously participated in the co-creation workshops, leveraging their familiarity with the project.

Phase 2 will involve the initial screening of identified families to verify their eligibility according to the study's inclusion and exclusion criteria. This verification will occur through various methods including phone or video calls to assess family interest and eligibility, screening during regular clinical visits, and collaborative work between researchers and clinicians who have direct access to families. Throughout this phase, each site will maintain an updated list of eligible families who meet all criteria for participation.

The recruitment process will start in Phase 3 and will be gradual and progressive, with formal enrollment of eligible families who choose to participate. This phase will start in August 2025. For each individual participant/family this phase begins with the signing of paper consent forms, with families retaining the information section while centers securely store the signed consent. Following enrollment, participant data is entered into the study database according to the data model established in WP 3, and participants are formally assigned to their respective cohorts based on their clinical profiles. After baseline measurements are completed,

an active retention strategy commences, featuring ongoing communication between clinical staff and enrolled families to minimize dropout and maintain participant engagement throughout the study period.

The recruitment strategy allows for adaptability across different clinical settings while maintaining methodological consistency. For example, centers may employ different approaches for recruiting children without being overweight/obese compared to the other cohorts. The process begins as soon as each pilot site receives ethical approval for the amended protocol and continues until the required sample size is achieved at each location, with particular attention paid to dropout monitoring and engagement strategies to maintain adequate study participation.

5 Regulatory and Ethical Considerations

5.1 Ethics Approvals

All Clinical sites secured ethics approval. The following table summarizes the approvals per site.

Table 2: Ethics Committee Approvals for BIO-STREAMS Project's Prospective Study

Date Approved or Submitted	Partner	Ethics Committee	Status	Reference
Approved: 25.04.2024	BLOCKS	Ethics Committee of the Specialized Hospital for Rehabilitation and Long-Term Treatment BLOCKS (SBRPL BLOCKS)	Approved	BLOCKS-2024-001
Part 1 (cocreation workshops) 12.02.2025; Part 2 (interventional study) 25.03.2025	CHUL	Ethics Committee of the CHU of Liege	Approved	2024/584; 2025/243
13/11/2024	KI	Swedish Ethical Review Authority	Approved	Ref. 2024-05917-01
14.11.2024	NKUA	Scientific Council of "Aghia Sofia" Children's Hospital, Athens, Greece	Approved	EB-PASCH-MoM: 14/11/2024, Re: PASCH-EIΣ-23716-27/09/2024
Approved 19.9.2024	PENTELE	Scientific Council of Children's Hospital PENTELE	Approved	10917/19-9-2024
Approved: 28.3. 2024	UKCM	Commission for Medical Ethics UKC Maribor	Approved	Ref. Number: UKC-MB-KME-17/24

Waiting approval	for	VHIR	Clinical Research Ethics Committee of University Hospital VALL D'HEBRON	Submitted	N/A
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5.2 Informed Consent

The informed consent process will be carried out during the onboarding of subjects. During the process a dialogue with participants will be opened. The recruitment process and strategy are explained in Appendix A: Detailed Study Protocol. Each clinical site will explain the nature of the study, the study's purpose, procedures, potential risks and benefits, and data protection measures through a detailed information letter tailored to both parents/guardians and children in age-appropriate language (see Appendix A: Detailed Study Protocol). For younger participants, a simplified version with accessible terminology is provided alongside the standard document. The consent process requires signed paperwork collected during the initial clinic visit, with the family keeping the information section while the clinical site securely stores the signed consent portion. For participants under the local age of consent (which varies by country), parental/guardian consent is mandatory, while older children may provide their own consent depending on local regulations. Assent is also obtained from younger children based on their ability to understand the project. The informed consent explicitly covers participation in the intervention, collection and use of biological samples (including saliva for genetic/epigenetic analysis), access to medical records, and permission for pseudonymized data sharing among project partners. Importantly, the consent materials emphasize the voluntary nature of participation, the right to withdraw at any time without consequences to standard care, and information about data protection measures implemented throughout the study.

5.3 Data Oversight

The study plans to process special categories of personal data (i.e. 'sensitive data') of children, which demands a strong emphasis on data oversight. To ensure compliance with ethical and legal obligations including the General Data Protection Regulation (GDPR), and to safeguard patient privacy, appropriate and state-of-the-art organisational and technical measures will be adopted. This includes the use of encryption technologies to ensure access to information about the study participants is limited to what is necessary to lawfully achieve the purposes of the study. All data processing will occur in the EU.

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5.3.1 Types of Personal Data

The personal data that is intended to be collected for the purposes of the study include:

- Secondary data from participants' personal medical records
- Primary data collected through participants' use of BIO-STREAMS mobile application (e.g. behavior, quality of life, activity using the ActiveHealth App and Serious Game suite; see section 2.8.2 for specific questionnaires)
- Primary data collected during the recruitment and baseline clinical data
- Primary data collected through the use of mobile devices
- Genetic data derived from saliva samples

5.3.2 Lawful basis

The lawful basis for processing of personal data will be informed and explicit consent given by children and/or legal guardians (depending on the minimal consent age according to clinical partners' national law).

Consent for data processing can be withdrawn by participants (and/or legal guardians) at any time before, during, or after the study.

5.3.3 Responsibility for processing

Clinical partners (listed below at section 5) are the entities responsible for determining the means and purposes of processing data throughout BIO-STREAMS. Therefore, clinical partners are the designated controllers that have chief responsibility for, and control over, observance of data protection principles and respect for data subject rights. Clinical partners may also, in certain instances in BIO-STREAMS, act as joint controllers where the means and purposes of processing are jointly determined by clinical partners.

Technical partners (listed below in section 6) will act as processors and can only process personal data under the authority of, and on behalf of, clinical partners acting as controllers.

Relevant Data Transfer (DTA) and Data Processing (DPA) Agreements, and Joint Controllorship Agreements will be signed among the BIO-STREAMS project partners as necessary to lawfully enable partners to process and share personal data necessary to achieve the purposes of the study.

Technical partners may engage sub-processors if necessary to process personal data upon written authorization of the controller.

5.3.4 Data subject rights

Clinical and technical partners will implement appropriate organizational and technical measures to ensure that data subject rights are respected.

The operationalization of rights to information and access (transparency), rectification (ensuring accuracy), erasure (right to be forgotten), objection, and explanation will be outlined in the Data Management Plan.

Consent forms, and an information letter for children and parents related to data processing, and a privacy notice are annexed to this protocol (Appendices 6 and 7).

5.3.5 Technical and Organizational Measures

BIO-STREAMS project will follow a ‘data protection by design and by default’ approach. In accordance with the GDPR, appropriate safeguards will be adopted to protect personal data throughout the lifecycle of the study. These measures will be presented during the ethical approval process at each participating institution.

The Security Assurance Framework (SAF) will ensure secure and privacy-preserving operation of all Bio-Streams components and services, dynamically operating both synchronously and asynchronously. Services include data audit, pseudonymization, anonymization and harmonization, along with the ML-assisted Synthetic Data Generator (SDG) used for anonymized data provision and algorithm training/testing

The BIO-STREAMS Node Bundle (BNB) will include the necessary computer resources for deployment and interconnection within the BIO-STREAMS Hub Network. This network ensures that the BIO-STREAMS Biobank is based on a decentralized federated data management system. The BNB will be installed at every BIO-STREAMS member site to create a Data Hub, where pseudonymized and standardized datasets are stored locally. All Hubs formulate the Hub Network constituting the BIO-STREAMS Biobank. Data processing tools for harmonization, curation and pseudonymisation will be integrated in the backend of BNBs. The connection with the Information Management System (IMS) will be established through associated Application Programming Interfaces (APIs). Security is guaranteed using industry-standard ssh public/private keys. No third-party authorities will be involved.

5.3.6 Pseudonymization

Only pseudonymized personal data, rather than directly identifiable data, will be available to BIO-STREAMS partners. The identifiers available to the BIO-STREAMS consortium are biological sex, age (but not birth date), country/region, and year of first diagnosis.

Only clinical partners (i.e. investigators) will retain the ability to directly identify data subjects from the pseudonymous datasets, for the purpose of ensuring data subject rights can be respected (e.g. opt-out, access rights), for the purpose of tracking and progress monitoring, and for the purposes of ensuring scientific integrity of the data processed.

The investigators will transfer the structured and pseudonymized data required for the study by applying pseudonymization tools to the data contributed by members of the BIO-STREAMS consortium who will use them.

Appropriate pseudonymization techniques and pseudonymization policies (i.e., deterministic pseudonymization, document-randomized pseudonymization, fully randomized pseudonymization) will be selected considering the data protection level, the utility of the pseudonymized dataset and the complexity associated to a certain scheme in terms of implementation and scalability (ENISA, Data Pseudonymization: Advanced Techniques and Use Cases) (ENISA, Deploying Pseudonymization Techniques). Both basic pseudonymization solutions (e.g., cryptographic hash function, message authentication code, symmetric encryption) and most advanced ones (e.g., Merkle trees, secure multiparty computation, secret sharing schemes) will be investigated according to data pseudonymization requirements.

5.3.7 Personal Data Sharing in Consortium

As described above, DPAs, DTAs, and Joint Controllorship Agreements will be signed among the BIO-STREAMS project partners as necessary to lawfully enable partners to process pseudonymized personal data.

5.3.8 Personal Data Sharing Outside Consortium

Only anonymized data will be shared with 3rd party researchers outside consortium under the Federated Data Storage paradigm (i.e. the BIO-STREAMS Node Bundle), hosted by BIO-STREAMS Information Management System, with access to be managed by a panel of experts.

5.3.9 Personal Data Retention

Personal data collected for the purpose of this clinical investigation will be kept in the BIO-STREAMS Information Management System indefinitely, or until the data subjects (or their legal guardians) initiate their right to be forgotten or withdraw their consent. This means that personal data will be stored and preserved for an extended period, ensuring that it remains extendable and available for future research and analysis. In accordance with the storage limitation principle, appropriate technical and organizational measures described in this protocol are to be implemented to safeguard the rights and freedoms of study participants. The need to retain personal data will be revisited iteratively by the panel of experts set up as part of the Information Management System no less than every 5 years after the completion of BIO-STREAMS.

5.4 Continued Monitoring and Risk Management

Continued ethical monitoring in clinical studies will involve oversight throughout the entire research lifecycle to ensure participant protection and data integrity remain prioritized from initial approval through study completion. To this end the BIO-STREAMS study implements a comprehensive framework for continuous monitoring and risk management to ensure participant safety and data integrity throughout the study period. The approach combines proactive surveillance with responsive action protocols tailored to the specific context of a digital intervention study involving children and adolescents. The details of the Adverse Effects Monitoring Protocol are outlined in Appendix.

The BIO-STREAMS consortium has identified the following key risks in the retrospective study:

Table 3: Key Risks Requiring Continued Ethical Monitoring in BIO-STREAMS Study

Risk Category	Specific Risks	Monitoring Approach	Mitigation Strategy	Responsible Party
Clinical Risks	<ul style="list-style-type: none"> Physical injury from sports activities Collapse during blood sampling Weakness/vomiting during OGTT test Occasional hypoglycemia between meals 	<ul style="list-style-type: none"> Regular check-ins during follow-up visits Immediate reporting of symptoms Monitoring of anthropometric data for concerning trends 	<ul style="list-style-type: none"> Appropriate medical intervention Temporary suspension of specific activities if needed Modification of recommended activities based on individual tolerance 	<ul style="list-style-type: none"> Clinical Site Principal Investigators Site Medical Staff
Psychological Risks	<ul style="list-style-type: none"> Increased anxiety or depression Disappointment with treatment results Self-aggressive behavior due to weight loss difficulties Increased body image concerns Weight stigma experiences 	<ul style="list-style-type: none"> Mental health screening at follow-up timepoints Monitoring of psychological questionnaire responses Passive monitoring of digital tool usage patterns 	<ul style="list-style-type: none"> Access to psychological support services Adjustment of recommendations to reduce pressure Enhanced positive reinforcement Education on realistic outcomes 	<ul style="list-style-type: none"> Clinical Site Investigators BIO-STREAMS Ethics Committee
Family Dynamic Risks	<ul style="list-style-type: none"> Parent-child conflict over adherence Excessive parental pressure 	<ul style="list-style-type: none"> Parent-child interaction assessment during visits 	<ul style="list-style-type: none"> Family counseling referrals 	<ul style="list-style-type: none"> Clinical Site Investigators

	<ul style="list-style-type: none"> • Family stigmatization • Household stress from behavior changes 	<ul style="list-style-type: none"> • Separate feedback sessions with parents and children • Monitoring of family engagement metrics 	<ul style="list-style-type: none"> • Parent education on supportive approaches • Family-focused intervention adjustments • Stress management resources 	<ul style="list-style-type: none"> • Family Support Specialists
Digital Intervention Risks	<ul style="list-style-type: none"> • Excessive screen time • Digital addiction behaviors • Unhealthy competition • Unrealistic goal setting through app 	<ul style="list-style-type: none"> • Usage pattern analysis • Time spent monitoring • Frequency of access tracking • Goal achievement rate monitoring 	<ul style="list-style-type: none"> • Usage time limits implementation • Balanced activity recommendations • Algorithm adjustments for realistic goals • Positive reinforcement for balanced use 	<ul style="list-style-type: none"> • Technical Partners • Clinical Manager • Scientific & Technical Manager
Data Privacy & Security Risks	<ul style="list-style-type: none"> • Data breach or unauthorized access • Re-identification of pseudonymized data • Unintended data sharing • Inappropriate use of genetic information 	<ul style="list-style-type: none"> • Security incident monitoring • Access logs review • Regular security testing • Data transfer tracking 	<ul style="list-style-type: none"> • Immediate containment of breaches • Enhanced encryption methods • Re-evaluation of access controls • Participant notification protocols 	<ul style="list-style-type: none"> • Project's DPO • BIO-STREAMS Ethics Committee • Technical Partners

<p>Incidental Findings Risks</p>	<ul style="list-style-type: none"> • Unexpected genetic findings • Previously undiagnosed conditions • Abnormal blood test results • Concerning behavioral patterns 	<ul style="list-style-type: none"> • Laboratory result review protocols • Genetic data screening • Clinical assessment at each timepoint 	<ul style="list-style-type: none"> • Established protocols for communicating findings • Referral pathways to specialists • Follow-up monitoring plans • Genetic counseling access 	<ul style="list-style-type: none"> • Clinical Site Principal Investigators • Clinical Coordinator
<p>Social & Environmental Risks</p>	<ul style="list-style-type: none"> • Socioeconomic barriers to adherence • Cultural conflicts with recommendations • Access inequality to digital tools • Environmental constraints to physical activity 	<ul style="list-style-type: none"> • Sociodemographic data analysis • Cultural acceptability assessment • Digital access monitoring • Environmental constraint reporting 	<ul style="list-style-type: none"> • Culturally adapted recommendations • Socioeconomic support resources • Alternative activity options • Community resource connections 	<ul style="list-style-type: none"> • BIO-STREAMS Ethics Committee • Clinical Site Teams
<p>Intervention Sustainability Risks</p>	<ul style="list-style-type: none"> • Post-study behavior regression • Dependency on digital tools • Loss of motivation after study • Withdrawal syndrome from study activities 	<ul style="list-style-type: none"> • Follow-up assessment after study completion • Transition monitoring • Post-intervention engagement tracking 	<ul style="list-style-type: none"> • Transition planning before study end • Sustainable habit formation focus • Community resource connections • Gradual intervention tapering 	<ul style="list-style-type: none"> • Clinical Coordinator • Clinical Site Investigators



5.4.1 Continuous Monitoring Procedures

The study employs a multi-tiered monitoring structure that integrates both automated and human oversight systems:

1. **Regular Participant Check-ins:** Study personnel conduct systematic assessments during follow-up visits (at timepoints T4, T5, and T6) to identify any emerging adverse events or concerns. These check-ins include specific questions about physical and psychological well-being related to study participation.
2. **Digital Intervention Usage Monitoring:** The BIO-STREAMS platform incorporates passive monitoring features that track user engagement patterns, with automated alerts for potential indicators of distress or disengagement. Significant changes in usage patterns trigger review by clinical site personnel.
3. **Adverse Event Logs:** Each clinical site maintains detailed documentation of all reported or observed adverse events using the standardized Adverse Event Report Form. These logs are reviewed monthly by each site's Principal Investigator and quarterly by the BIO-STREAMS Ethics Committee.
4. **Data Quality Surveillance:** Regular data quality checks are conducted to identify anomalies or inconsistencies that might indicate technical issues affecting the integrity of collected information or participant experience.

5.4.2 Risk Management Strategy

The risk management approach focuses on both prevention and response:

1. **Preventive Measures:**
 - Continuous re-evaluation of risk levels for each participant during study participation
 - Regular training updates for all study personnel on adverse event identification and reporting procedures
 - Proactive engagement with participants showing signs of disengagement to address concerns before they escalate
2. **Response Protocols:**
 - Clearly defined escalation pathways for different categories of adverse events, with response timelines of 5-7 days for non-serious events and 48 hours for serious adverse events
 - Immediate intervention for any indicators of psychological distress (including disappointment with results, depression, or self-aggressive behavior)

- Access to counseling or appropriate support for participants experiencing adverse events

3. Ongoing Risk Assessment:

- Quarterly review of all reported adverse events by the BIO-STREAMS Ethics Committee to identify patterns requiring protocol adjustments
- Regular evaluation of the risk-benefit profile of study participation for different participant cohorts
- Adaptation of monitoring intensity based on observed risk patterns

5.4.3 Governance and Oversight

The continued monitoring and risk management activities are overseen by a structured governance framework:

1. **Local Oversight:** Principal Investigators at each clinical site serve as the first line of monitoring, with responsibility for immediate response to adverse events within their participant populations.
2. **Centralized Review:** The BIO-STREAMS Ethics Committee conducts regular reviews of monitoring data across all sites to ensure consistency and identify inter-site variations requiring attention.
3. **Expert Consultation:** The External Advisory Board provides periodic independent assessment of monitoring procedures and risk management approaches, with particular focus on ethical considerations specific to pediatric participants.

Conclusions

The BIO-STREAMS study defined a multifaceted approach towards obesity prevention that combines state-of-the-art digital technologies with rigorous scientific methodology. This study initiation package has outlined the framework for a mixed-methods investigation that will evaluate personalized digital interventions for obesity prevention, incorporating genetic, epigenetic, and behavioral factors across seven clinical sites in six European countries.

The study's design, encompassing both co-creation workshops and an intervention component, ensures that the developed solutions are not only scientifically valid but also user-centered, ethically sound, and culturally sensitive. By stratifying participants into three distinct cohorts—children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM), and children with overweight/obesity with metabolic abnormalities (COMA)—the study will provide valuable insights into the differential impact of interventions across diverse populations.

The BIO-STREAMS technological ecosystem, featuring the ActiveHealth App, Serious Games Suite, and Micro-moments approach, represents a novel integration of digital tools designed to enhance engagement and facilitate sustainable behavior change. These components are supported by a robust data governance framework that prioritizes participant privacy and data security while enabling scientific discovery.

Throughout the study, comprehensive monitoring procedures and risk management strategies will be implemented to safeguard participants' wellbeing and ensure data integrity. The multi-tiered governance structure, involving clinical partners, technical experts, and ethics advisors, will provide continuous oversight of all study activities.

As the BIO-STREAMS project proceeds through its planned timeline from 2024 to 2027, it aims to generate valuable evidence on the efficacy of personalized digital interventions for childhood obesity prevention and management. The findings will contribute to the scientific literature, inform clinical practice, and potentially shape public health policies aimed at addressing the childhood obesity epidemic across Europe and beyond.

Through its innovative approach and rigorous methodology, the BIO-STREAMS study stands to make a significant contribution to our understanding of childhood obesity and provide practical solutions for prevention and management that can be implemented across diverse healthcare settings.

6 Appendix A: Detailed Study Protocol

Feasibility Study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Study

Clinical Study Protocol	
Clinical protocol number	ISRCTN, 46980
Document version	2.0
Clinical investigation Title	Feasibility Study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Approach
Novel solution	Digital technology – BIO-STREAMS – Childhood Obesity Platform: Knowledge base and Predictive/Prognostic AI systems - Serious Games
Organization responsible for clinical investigation (S)	Names will be given per site
Principal Investigator of the Pilot Center	Names will be given per site
Coordinating investigator (CI)	Dr. Izidor Mlakar, University of Maribor

6.1.1 Document History

Revision	Date of enactment	Change author	Change description
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1.1	23.04.2024	Izidor Mlakar, Ana Rehberger	Second Draft of the Protocol
1.2	7.6.2024	All PIs	Third draft of the protocol
1.3	27.06.2024	All Partners	Refinements to the protocol
1.4	19.7.2024	All Partners	Major comments and dilemmas resolved, first draft of the final protocol
1.5	26.7.2024	Ana Rehberger, Izidor Mlakar	Final protocol to be translated into piloting languages
2.0	11.3.2025	Ana Rehberger	Final protocol with changes for amendment – in comments or track changes

6.1.2 Table of Contents

Abbreviations	11
1 Introduction	13
1.1 Scope of Project	13
1.2 Scope of Report	16
2 Study Overview	18
3 Study Information	25
3.1 Background.....	25
3.2 Study Objectives.....	25
3.3 Intervention	26
3.4 Study and Execution Plan.....	27
3.4.1 Overall study execution	27
3.4.2 Intervention Timeline (participant level design)	28
4 Recruitment Strategy	30
5 Regulatory and Ethical Considerations	32
5.1 Ethics Approvals	32
5.2 Informed Consent	33
5.3 Data Oversight.....	33
5.3.1 Types of Personal Data	33
5.3.2 Lawful basis	34
5.3.3 Responsibility for processing	34
5.3.4 Data subject rights	34
5.3.5 Technical and Organizational Measures	35
5.3.6 Pseudonymization	35
5.3.7 Personal Data Sharing in Consortium	35
5.3.8 Personal Data Sharing Outside Consortium.....	36
5.3.9 Personal Data Retention.....	36
5.4 Continued Monitoring and Risk Management	36
5.4.1 Continuous Monitoring Procedures	42
5.4.2 Risk Management Strategy	42
5.4.3 Governance and Oversight.....	43
Conclusions	44
6 Appendix A: Detailed Study Protocol	45



6.1.1 Document History46

6.1.2 Table of Contents47

6.1.3 Executive Summary.....51

6.2 General Information56

6.2.1 Study Rationale56

6.2.2 Current Knowledge and Background.....58

6.2.3 Research Questions & Hypothesis62

6.2.4 Primary and Secondary Aims and Outcomes.....63

6.3 Study Design64

6.3.1 Sample Size Justification.....65

6.3.2 Study Population.....67

6.3.3 Timing of the Study Procedures71

6.3.4 Description of Study Procedures73

6.3.5 Data Analysis82

6.4 BIO-STREAMS Technological Components85

6.4.1 BIO-STREAMS Federated Biobank: A Collection of Node Bundles86

6.4.2 BIO-STREAMS Information Management System.....86

6.4.3 BIO-STREAMS Dashboard87

6.4.4 BIO-STREAMS ActiveHealth App88

6.4.5 BIO-STREAMS Serious Games Suite.....89

6.4.6 BIO-STREAMS Risk Assessment and Recommendation Engine.....89

6.4.7 BIO-STREAMS Micro-moments90

6.5 Data Flow, Data Operations and Data Procedures91

6.5.1 Data Oversight.....91

6.5.2 Categories of Personal Data92

6.5.3 Legal Basis92

6.5.4 Data Collection93

6.5.5 Data Sharing and Responsibility of Processing93

6.5.6 Data Subjects' Rights95

6.5.7 Data Storage.....95

6.5.8 Data Harmonization & Data Curation95

6.5.9 Data Retention97

6.5.10 Security Measures97

6.6	Study Quality Control Procedures	98
6.6.1	Study Deviation and Changes	98
6.6.2	Methodological Guidelines and Standards	98
6.6.3	Data Review and Processing	99
6.6.4	Study Suspension or Early Termination	99
6.6.5	Study Close-out	100
6.6.6	Data Reporting and Publication	100
6.6.7	Adverse Effects Monitoring and Reporting	100
6.7	Pilot Sites	101
6.8	Data Processors for the Intervention Study	104
6.9	Study financing	108
6.10	Appendices	109
6.10.1	Co-creation Workshop Materials	110
	Appendix 1: Child Persona Description	110
	Appendix 2: Questions for Input on Child Persona	112
	Appendix 3: Questions for Input on User Requirements, Study Design and Intervention	112
	Appendix 4: BIO-STREAMS ActiveHealth App Mock-ups	115
	Appendix 5: Serious Games mock-ups	119
	Appendix 6: Consent form Package for Co-creation Workshops	120
6.11	Intervention Study Materials	131
	Appendix 7: Consent form Package for the Intervention Study	131
7	Appendix B: Recruitment Strategy	144
7.1	Recruitment Strategy	144
7.1.1	Phase 1: Building a List of Interested Participants/Families	144
7.1.2	Phase 2: Initial Screening of Families	146
7.1.3	Phase 3: Formal Enrollment	146
7.1.4	Special Considerations	146
8	Appendix C: Standard Operating Procedures for the Prospective Study	148
8.1	GENERAL INFORMATION	151
8.1.1	Purpose of the Protocol	151
8.1.2	Scope of the Protocol	151
8.2	Roles and Responsibilities	152
8.3	REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE CLINICAL COORDINATOR	154

8.3.1 “Serious adverse event” 154

8.3.2 Severity assessment..... 155

8.3.3 Timelines 156

8.3.4 Immediate reporting and follow-up report..... 156

8.3.5 Non-immediate reporting 156

8.3.6 Start and end of reporting serious adverse events to the sponsor..... 156

8.3.7 Determining causality 156

2.5 Foreseen workflow of reporting of adverse events 159

8.4 REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE BIO-STREAMS SOP COMMITTEE 160

8.5 REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE INVESTIGATORS 160

8.5.1 “Adverse reactions” 160

8.6 ADVERSE EVENTS REPORTING IN VARIOUS STUDY PHASES AND MODES..... 160

8.6.1 Recruitment 160

8.6.2 Study execution 161

Appendix 161

Adverse Events Report Form..... 161

9 Appendix D: Self-report Outcome Measures..... 164

List of Figures

Figure 1: A visual representation of BIO-STREAMS Ecosystem..... 14

Figure 2: Process of collecting, storing, analyzing, and sharing Project data 16

Figure 3: Prospective Study Overall Timeline, *M refers to the month of the project and not the study.27

Figure 4: Prospective Study Timeline of the intervention28

Figure 5: Intervention study data collection timeline 75

Figure 6: BIO-STREAMS technological components85

Figure 7: Child Persona Description 112

Figure 8: BIO-STREAMS ActiveHealth App mock-ups..... 118

Figure 9: Let’s move, Food quiz, and Fruit ninja mock-ups 119

Figure 10: Recruitment Leaflet Designed for The Study, Part 1. 145

Figure 11: Recruitment Leaflet Designed for The Study, Part 2. 146

List of Tables

Table 1: Subject distribution per cohort and pilot site (intervention study)66

Table 2: Subject distribution per cohort and piloting country (co-creation workshops)67

Table 3: The IDF definition of metabolic parameters in children and adolescents70

Table 4 : A list of al collected measurements in the Intervention Study78

Table 5: A list of outcomes, measuring instruments, number of items, and time points of collection ...79

Table 6: Summary of targeted initial analyses82

6.1.3 Executive Summary

Title	Feasibility study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Study
Co-creation Workshop aims	<ul style="list-style-type: none"> (1) To re-evaluate the Personas and refine user-requirements and stories based on feedback from real-world subjects. (2) To refine the digital interventions to ensure adherence and sustainability.

	<p>(3) To refine the study to ensure minimal dropout and maximal output with minimal possible effort from the end-subjects.</p>
<p>Intervention study aims</p>	<p>Primary aims:</p> <ol style="list-style-type: none"> (1) To evaluate the impact of genetic predisposition and epigenetic modifications on efficacy of behavior modification. (2) To evaluate the acceptance and impact of BIO-STREAMS recommendation tools and micro-moment-based interventions for lifestyle modifications on awareness and engagement in preventive behaviors of children, adolescents, and families. <p>Secondary aims:</p> <ol style="list-style-type: none"> 1) To identify similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications differentiating between children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM) and children with overweight/obesity with metabolic abnormalities (COMA) 2) To empower parents and children to prevent obesity through new tools and services for informed decisions about lifestyle choices. 3) To evaluate the possible benefits of the recommendation tool towards health outcomes in children & adolescents by evaluating the improvement in health/food literacy, quality of life and well-being, increase of self-regulation and decrease in mental distress, including anxiety, depression, and self-perceived stigma 4) To analyze the impact of personalized risk assessment on preventive behavior (i.e. following the recommendations) of children and families. 5) To quantify medical costs related to overweight/obesity management
<p>Intervention study outcomes</p>	<p>Primary outcomes:</p> <ol style="list-style-type: none"> (1) Number of new biological pathways conferring efficacy of preventive behavior. (2) Acceptability and usability of the of the mobile application and interventions measured through affective attitude (user experience) and participant engagement, trust and acceptance, perceived burden of the behavior modifications and adherence <p>Secondary outcomes:</p> <p>A list of outcomes to be measured with instrument abbreviations in parentheses:</p> <ol style="list-style-type: none"> 1. Sensitivity and specificity of defining the subsets of patients at risk

	<p>for metabolic dysfunction.</p> <ol style="list-style-type: none"> 2. Reduction in body weight of 5% or centiles of BMI by 5 percentile points or z-score BMI change by 0,25, reduction in bodyfat, reduction in other anthropometric parameters. 3. Improvement of health/food literacy (FNLIT). 4. Improvement in quality of life (KIDSCREEN-10). 5. Improvement in well-being (WHO-5). 6. Increase in self-regulation (SRQ and SREBQ). 7. Decreased mental distress, including anxiety (PSWQ-C) and depressive symptoms (CES-D). 8. Decreased self-perceived stigma (WSSQ). 9. Medical costs related to overweight/obesity management.
Co-creation workshops design	<p>Co-creation workshops with open discussion on the topics related to the aims of the co-creation led by moderators. Group activity with similarly aged 6-8 children in each group: minimum 144 participants in total, from different age groups (minimum 36 participants per age-group in total; (i) up to 8 years, (ii) 8-10 years, (iii) 10-14 years, (iv) 14-18 years) and cultural settings (minimum 24 participants per piloting county).</p>
Intervention study design	<p>3 arms: children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM) and children with overweight/obesity with metabolic abnormalities (COMA), 6 time points, 2 times saliva sampling and centralized analysis (saliva-centrally), 1 time blood (in case no data not older than 1 year is already available)</p>
Duration of clinical investigation	<p>Overall duration: 31 months (co-creation 6 months), intervention per subject 6 months, final follow up 1 month after intervention)</p>

<p>Subject population</p>	<p>Co-creation workshops:</p> <p>A workshop per pilot per group in two parts (1h 30 mins each) including same participants.</p> <p>144 participants in total (pilot sites all together), from different age groups (minimum 36 participants per age-group in total; (i) up to 8 years, (ii) 8-10 years, (iii) 10-14 years, (iv) 14 -18 years) and 6 cultural settings (minimum 24 participants per piloting country) to ensure effective engagement, collaboration, and diverse perspectives. 48 CWO, 48 CONM and 48 COMA will be included in the co-creation workshops during the first part of the study.</p> <p>Intervention study:</p> <p>350 in CWO group, 350 in CONM group and 350 COMA group to be included in the intervention, from 7 clinical sites (UKCM, NKUA, KI, BLOCKS, VHIR, CHUL, PENTELI). to account for the minimum sample size per group</p>
<p>Number of Sites</p>	<p>7 clinical sites:</p> <ol style="list-style-type: none"> 1) UKCM (Slovenia) 2) NKUA (Greece) 3) KI (Sweden) 4) BLOCKS (Bulgaria) 5) VHIR (Spain) 6) CHUL (Belgium) 7) PENTELI (Greece)
<p>External organizations involved in the clinical investigation</p>	<p>No organizations external to the BIO-STREAMS consortium will be involved in the clinical investigation. Each clinical site, contributing with participants, will allocate a pilot leader (e.g. the Principal Investigators) how will oversee the local study and to oversee the operations within the pilot study. Project’s Clinical Manager, Izidor Mlakar (University of Maribor) will oversee the execution of all the studies. Oversight of the Data Operations will be carried out by Magdalena Góralczyk, Peter Davis and Lucrezia Nicosia (White Label Consultancy APS) and the Project’s Data Protection Officer, Dimitris Kalogeras (ICCS). Each clinical partner also has their own DPO (contact details of each provided below).</p>
<p>Data Oversight</p>	<p>Co-creation workshops</p>

	<p>In observance with data protection by design and default principles, the workshop plans to process the minimum personal data necessary to achieve its purposes. The aim of the workshop is not to gather granular information about the workshop participants, but rather, high-level feedback about the proposed intervention study.</p> <p>The data controller for the processing of workshop data is the clinical partner carrying out the workshop. Only anonymized (aggregated) data will be shared with other BIO-STREAMS partners and those outside of the BIO-STREAMS consortium.</p> <p>Intervention study</p> <p>The study plans to process special categories of personal data (i.e. ‘sensitive data’) of children, which demands a strong emphasis on data oversight. To ensure compliance with ethical and legal obligations including the General Data Protection Regulation (GDPR), and to safeguard patient privacy, appropriate and state-of-the-art organizational and technical measures will be adopted. This includes the use of encryption technologies to ensure access to information about the study participants is limited to what is necessary to lawfully achieve the purposes of the study. All data processing will occur in the EU.</p> <p>The data oversight measures include:</p> <ul style="list-style-type: none"> ➤ Appropriate organizational and technical measures to ensure compliance with ethical and legal obligations including GDPR ➤ Encryption technologies limit access to participant information to what is necessary for the study purposes ➤ Data processing exclusively within the European Economic Area and Switzerland ➤ Clinical partners acting as data controllers, determining the purposes and means of processing ➤ Technical partners acting as data processors, operating under the authority of clinical partners ➤ Data Transfer Agreements (DTA), Data Processing Agreements (DPA), and Joint Controllership Agreements implemented as needed ➤ The BIO-STREAMS Node Bundle (BNB) ensuring a decentralized federated data management system where pseudonymized and standardized datasets are stored locally ➤ Only pseudonymized personal data available to BIO-STREAMS partners ➤ Clinical partners retaining the ability to directly identify participants from pseudonymized datasets
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	<ul style="list-style-type: none"> ➤ Personal data stored indefinitely or until participants initiate their right to be forgotten or withdraw consent, with periodic reviews at least every 5 years
Clinical investigation financing	This Clinical study is part of the BIO-STREAMS European Project funded within the research and innovation program of the Horizon Europe under N° 101080718. The funding source had no impact on the decision to carry out the study or in its design. The funding source will have no impact on the decisions related to publishing this research or its outcomes. The content of this document does not reflect the official opinion of the European Union or any other institution.
Person paying compensation for costs and time incurred in participating in a clinical investigation, procedure and conditions for calculation and payment of compensation	No compensationis provided.

6.2 General Information

6.2.1 Study Rationale

Obesity represents one of the most challenging public health problems of the 21st century owing to both its epidemic proportions worldwide and the associated significant morbidity and mortality. During the last four decades, the prevalence of overweight and obesity in childhood and adolescence has risen substantially in most high-income countries and appears to be rising rapidly in low- and middle-income countries, as well. According to the World Health Organization (WHO), 41 million children under the age of 5 years and more than 340 million children and adolescents aged 5–19 years are estimated to be overweight or obese.

While obesity can occur throughout the lifespan, it can have its origins during fetal development and infancy and is thus affected by changes in epigenetic regulation or developmental programming of gene expression. Psychological and social determinants also influence the risk for obesity either alone or in interaction with other causes of obesity. Differences in socioeconomic parameters including economic, education, social and community context, health and health care, and neighborhood and built environment have significant roles in weight gain. Obesity, in turn,

can elicit reactions of social stigma and discrimination that can arise when children or adults do not fit social norms for body weight or shape.

Genetic predisposition and epigenetic modifications play a role in the efficacy of behavior modification in obesity prevention and treatment. Recent progress in epigenetics of obesity has been made, with preliminary evidence from animal and human studies supporting the effect of epigenetics on obesity¹³. DNA methylation is the most investigated epigenetic mechanism, and studies have reported the differential expression status of multiple genes before and after obesity interventions. The identification of epigenetic markers of obesity detectable at birth has the potential to predict obesity risk and inform treatment and prevention strategies. Additionally, environmental exposure, including exposure to malnutrition, is associated with methylation changes and has the potential to influence adult phenotypes, suggesting that transient environmental effects experienced early in life may lead to permanent effects in the form of epigenetic modifications¹⁴. Epigenetic markers could improve the success of weight loss treatment in the context of precision nutrition. The association between histone modifications and obesity in humans is less studied, but some current results suggest an association between genome-wide histone modifications and obesity¹³. Overall, the findings support the underlying epigenetic programming of obesity and comorbidities, and ongoing research is necessary to establish true cause-effect relationships between epigenetic markers and obesity¹⁵.

Moreover, recent research suggests that clinical presentation, personal exposome, genetic predisposition, and epigenetic modifications differ between metabolically healthy and metabolically unhealthy individuals and those at risk for metabolic dysfunction. Metabolically unhealthy individuals have a higher risk of developing metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular disease, due to genetic predisposition and epigenetic modifications. In this study, we will focus on primary childhood overweight/obesity or metabolically unhealthy obesity (i.e. obesity with comorbidities, such as hypertension, dyslipidemia and diabetes mellitus), contrary to the secondary childhood overweight/obesity or metabolically unhealthy obesity attributed to endocrine or genetic disorders.

With increasing volumes and greater access to data in electronic formats, it is unsurprising that researchers are beginning to apply big data to key concerns including mental health¹⁶, infectious

¹³ Wu, F. Y., & Yin, R. X. (2022). *Recent progress in epigenetics of obesity. Diabetology & Metabolic Syndrome, 14*(1), 171.

¹⁴ Rohde, K., Keller, M., la Cour Poulsen, L., Blüher, M., Kovacs, P., & Böttcher, Y. (2019). *Genetics and epigenetics in obesity. Metabolism, 92*, 37-50.

¹⁵ Smith, E. N., Chandanathil, M., Millis, R. M., & Smith, E. N. (2023). *Epigenetic mechanisms in obesity: broadening our understanding of the Disease. Cureus, 15*(10).

¹⁶ Stewart R, Davis K. 'Big data' in mental health research: current status and emerging possibilities. *Soc Psychiatry Psychiatr Epidemiol.* 2016;51:1055–72.

disease¹⁷ and healthcare¹⁸. In the field of obesity research, there is a long history of using routine data sources to track the prevalence of the disease, as well as identify risk factors. Supplementing this with new forms of data has the potential to broaden our understanding of obesity, bringing together information from different facets of environment and behaviors¹⁹. BIO-STREAMS aims to deliver a Multi-Pillar Framework to address childhood obesity by building on an EU biobank, micro-moments and mobile recommendation systems. To this end, BIO-STREAMS mobilizes a diverse group of partners with clear in-project duties to design, create and deploy the following in multiple settings involving 7 hospitals in 6 EU countries and 5 school sites in 5 EU countries: The first EU Childhood/Adolescence Obesity Biobank (EU data space – BIO-STREAMS Biobank) acting as an EU-wide data-sharing center for research and innovation, hosting real and synthetic data and ensuring:

- Standardized data collection, exploiting knowledge from European Core Health Indicators
- Data model with demographic, behavioral, clinical, genetic/epigenetic and cost data
- Expandable Data Network hosting diverse datasets across countries via EU-wide local hubs
- Knowledge Hub with group-specific policies (for health professionals, schools and citizens), best practices and research outcomes, regularly updated upon entry and analysis of new data within the BIO-STREAMS Biobank
- Personalized Risk-Assessment for adverse metabolic outcomes attributed to obesity
- Recommendation Engine generating tailored programs for prevention and healthy living, following a family centric approach and considering micro-moments as determinants driving behavior and adherence
- Evidence-based knowledge communication to stakeholders via transparent methods for analysis & reporting

6.2.2 Current Knowledge and Background

Overweight and obesity are the leading lifestyle-related causes of clinical and public health concerns. Health behavior change is central in obesity management. Namely, lifestyle behaviors associated with weight status (i.e. dietary intake and physical activity), tend to track from childhood to adulthood. Hence prompt identification and screening for pediatric overweight and obesity can help lead to early interventions and decrease associated medical comorbidities. Interventions to prevent pediatric obesity are therefore crucial for securing public health currently and in the future.

Overall, body weight is influenced by genetic, metabolic, behavioral, environmental, cultural and socio-economic factors²⁰. Childhood obesity is a complex health issue that arises from the interplay of genetic predisposition, environmental factors, and lifestyle choices. **Genetic factors**

¹⁷ Hay SI, George DB, Moyes CL, Brownstein JS. Big data opportunities for global infectious disease. *PLoS Med.* 2013;10:e1001413

¹⁸ Raghupathi W, Raghupathi V. Big data analytics in healthcare: promise and potential. *Health Inf Sci Syst.* 2014;2:3.

¹⁹ Timmins, K. A., Green, M. A., Radley, D., Morris, M. A., & Pearce, J. (2018). How has big data contributed to obesity research? A review of the literature. *International journal of obesity*, 42(12), 1951-1962.

²⁰ Behavioural interventions for preventing and treating obesity in adults. Sharma M. *Obes Rev.* 2007;8:441–449



can contribute to a child's susceptibility to obesity, but they only account for a small percentage of cases. The primary causes of childhood obesity are environmental, and lifestyle related. **Diet** plays a significant role in childhood obesity. The increased consumption of processed foods, sugary drinks, and larger portion sizes has led to a higher calorie intake among children. Aggressive advertising practices and the low cost of energy-dense foods drive children towards unhealthy food choices. School cafeterias and fast-food shops near schools often provide easy access to high-calorie foods, contributing to unhealthy eating habits. **Physical activity** levels have also declined due to increased screen time and urbanization. Children spend more time indoors on televisions, the internet, and computer games, reducing their engagement in outdoor play. In many developing countries, there is a lack of open spaces and playgrounds in schools and communities, making it difficult for children to participate in physical activities. Increasing pressure on academic performance and reduced emphasis on physical activity in schools further contribute to this issue. **Socioeconomic factors**, such as poverty and limited access to healthy foods and safe spaces for exercise, also play a significant role in childhood obesity. Urban poor in developed countries and urban rich in developing countries are both at risk for different reasons. In addition, increased availability of domestic help, traveling to school by car, and cultural beliefs about food and physical activity all contribute to childhood obesity. In conclusion, while genetic predisposition can increase a child's susceptibility to obesity, environmental factors and lifestyle choices are the primary drivers of this health issue. Diet, physical activity, and socioeconomic factors all play a significant role in the development and prevention of childhood obesity.

Overweight and obesity is mainly the result of a sedentary lifestyle and a positive balance between energy consumption and expenditure⁷. However, the etiology of obesity can be observed from a clinical and public health perspective. The clinical perspective is based on individual variations (genetic and biologic variations), while the public health perspective is based on calorie intake and energy expenditure⁷. Despite major evidence for an important role of environmental factors, such as sedentary lifestyle combined with intake of energy dense nutrition, there is no doubt for a strong genetic basis of common (polygenic) obesity. Over the last two decades, efforts in identifying and replicating genetic variants predisposing individuals to common (polygenic) forms of obesity were largely characterized by slow progress and limited success, in sharp contrast to the successful gene identification in monogenic and syndromic forms of obesity²¹. Genome-Wide Association Studies (GWAS) revealed important novel insights into genetics of obesity, however, a major limitation in understanding the genetic contribution is owed to the large proportion of unexplained variability of BMI, as identified Single Nucleotide Polymorphism (SNP) markers collectively explain less than 3%–5% of the observed variability²². In that context, epigenetics that rely on a dynamic interaction between the environment and the individual genetics offers a more promising explanatory context for variability than genetics alone, but well-designed studies are still lacking. Furthermore, in addition to genetics, it is also crucial to achieving a sustainable

²¹ Rohde, K., Keller, M., la Cour Poulsen, L., Blüher, M., Kovacs, P., & Böttcher, Y. (2019). Genetics and epigenetics in obesity. *Metabolism*, 92, 37-50.

²² Yengo, Loic, Julia Sidorenko, Kathryn E. Kemper, Zhili Zheng, Andrew R. Wood, Michael N. Weedon, Timothy M. Frayling et al. "Meta-analysis of genome-wide association studies for height and body mass index in ~ 700000 individuals of European ancestry." *Human molecular genetics* 27, no. 20 (2018): 3641-3649.



balance between energy output and input. The concept of energy balance is crucial in the context of weight management and obesity. When an individual is in energy balance, energy intake equals energy expenditure, and weight should remain stable²³.

The challenge of choosing which feature interactions to study is a barrier to gaining new insights into the principles of how different exposures in the exposome interact to shape health. This is because the traditional prediction tools often lack consideration of nonlinear, collinear and interactive effects among factors²⁴. A wide panel of machine-learning and deep-learning models has been developed to facilitate the characterization of these effects²⁵. Artificial Intelligence (AI) and Machine Learning (ML) represent a promising pathway towards timely and accurate screening and diagnosis. Namely, AI (i.e. non-knowledge-based systems) can represent a unique opportunity to address the heterogeneity in the pathophysiology and diagnosis by harnessing big data and discover new complex patterns in high-dimensional data well beyond human performance²⁶. In fact, medical support based on Artificial Intelligence is the modern way to tackle complex problems faced in the medical field. AI provides smart ways to manage medical demand. There have been various studies conducted in academic literature which gives us an idea of the importance of AI in the healthcare sector in enhancing service quality. AI can improve medical treatment or diagnosis, e.g., HIV drug resistance prediction²⁷, breast cancer prediction²⁸, or type 2 diabetes mellitus (T2DM)²⁹, however, these models cannot be used in an automated and unsupervised manner. In healthcare, where mistakes can cost human life, the unexplainable (i.e., black box) nature of AI makes it less acceptable for clinicians and regulators³⁰.

Finally, the challenges related to adherence to recommendations and behavioral modifications in children with overweight and obesity are multifaceted. Adherence to behavioral modifications, such as dietary changes and increased physical activity can be challenging for children with obesity³¹. Factors that can affect adherence to behavioral modifications in children with obesity include parental involvement, family dynamics, cultural beliefs, and socioeconomic factors. Interventions that involve the whole family and address the social and environmental factors that contribute to obesity may be more effective in promoting adherence to behavioral modifications and achieving long-term weight management in children with obesity. Behavioral interventions for weight management should specifically target different components of the COM-B model, including physical and psychological capability (C), social and physical opportunity (O), and

²³ Hill, J. O., Wyatt, H. R., & Peters, J. C. (2013). The importance of energy balance. *European endocrinology*, 9(2), 111.

²⁴ P. Doupe, J. Faghmous, S. Basu, Machine learning for health services researchers. *Value Health* 22, 808–815 (2019)

²⁵ C. Colmenarejo. Machine learning models to predict childhood and adolescent obesity: a review. *Nutrients* 12, 2466 (2020)

²⁶ Fazi MB. Beyond Human: Deep Learning, Explainability and Representation. *Theory, Culture and Society*; 38. Epub ahead of print 2021. DOI: 10.1177/0263276420966386.

²⁷ Riemenschneider, M., Hummel, T., & Heider, D. (2016). SHIVA-a web application for drug resistance and tropism testing in HIV. *BMC bioinformatics*, 17(1), 1-6.

²⁸ Montazeri, M., Montazeri, M., Montazeri, M., & Beigzadeh, A. (2016). Machine learning models in breast cancer survival prediction. *Technology and Health Care*, 24(1), 31-42.

²⁹ Talaei-Khoei, A., & Wilson, J. M. (2018). Identifying people at risk of developing type 2 diabetes: a comparison of predictive analytics techniques and predictor variables. *International journal of medical informatics*, 119, 22-38.

³⁰ Shortliffe EH, Sepúlveda MJ. Clinical Decision Support in the Era of Artificial Intelligence. *JAMA - Journal of the American Medical Association*; 320. Epub ahead of print 2018. DOI: 10.1001/jama.2018.17163.

³¹ Olateju, I. V., Ogwu, D., Owolabi, M. O., Azode, U., Osula, F., Okeke, R., & Akabalu, I. (2021). Role of behavioral interventions in the management of obesity. *Cureus*, 13(9).



automatic and reflective motivation (M)³². Self-efficacy and self-esteem may play a significant role in individual capabilities, opportunities, and reflective motivation and should be included in tailored public health interventions. Health programs focusing on addressing poor health in younger people may help to promote sustainable behavior change among people affected by overweight³².

There are 1113 interventional studies registered on ClinicalTrials.gov³³ addressing behavior intervention in obese children. 514 address dietary intervention³⁴, 799 address physical activity³⁵ and 395³⁶ both. Only 11 of them include genetics³⁷ and 4 include epigenetics³⁸. Finally, o^{39[ob]}. In this study a comprehensive therapeutic nutrition intervention program based on a slightly hypocaloric Mediterranean Diet (MD) along with increased physical activity in children with central obesity (7-16 years old) was applied. The effectiveness of this program will be evaluated by assessing changes in body composition, lifestyle and biological and molecular parameters (genetic and epigenetic). The study, however, specifically focuses on Mediterranean diet and includes only obese children.

Overall, most studies are interventional, but only some of them are randomized. 46 studies registered in ClinicalTrials.gov include behavior intervention and smartphone application⁴⁰. Most studies are focused on weight loss and only 5 address perceptions and attitudes⁴¹. However, none of the studies focus on identifying the biomarkers of metabolically healthy and metabolically unhealthy obese/overweight or the impact of genetic predisposition and epigenetic modification on the efficacy of behavior interventions. Furthermore, while most of the studies specifically exclude metabolically unhealthy children with obesity, our study will include primary childhood overweight/obesity or metabolically unhealthy obesity with comorbidities.

³² Timkova, V., Minarikova, D., Fabryova, L., Buckova, J., Minarik, P., Katreniakova, Z., & Nagyova, I. (2024). Facilitators and barriers to behavior change in overweight and obesity management using the COM-B model. *Frontiers in Psychology*, 15, 1280071.

³³https://clinicaltrials.gov/ct2/results?term=behaviour+intervention&cond=Obese&age_v=&age=0&gndr=&type=Intr&rslt=&Search=Apply

³⁴<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+diet&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

³⁵<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+activity&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

³⁶<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+activity+diet&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

³⁷<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+activity+diet+genetics&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

³⁸<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+activity+diet+epigenetics&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

³⁹<https://clinicaltrials.gov/ct2/show/NCT03147261?term=behaviour+intervention+activity+diet+epigenetics+genetics&type=Intr&cond=Obese&age=0&draw=2&rank=1>

⁴⁰<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+smartphone+application+&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>

⁴¹<https://clinicaltrials.gov/ct2/results?cond=Obese&term=behaviour+intervention+smartphone+application+Perception+and+Attitudes&cntry=&state=&city=&dist=&Search=Search&type=Intr&age=0>



6.2.2.1 Current Gaps

Current research indicates a lack of comprehensive understanding regarding the relative impact of various risk factors contributing to childhood overweight and obesity within specific populations⁴². Studies have highlighted disparities in obesity prevalence among different racial and ethnic groups, emphasizing the need for more targeted research to identify the specific risk factors affecting these populations⁴³. Limited data exist on how genetic predisposition, environmental influences, lifestyle choices, and socioeconomic factors interact to influence obesity rates in diverse populations, hindering the development of tailored interventions^{44,45,46}.

The long-term effectiveness of preventive strategies aiming at reducing childhood overweight and obesity remains a gap in current knowledge. While population-based approaches have been shown to be most effective in preventing childhood obesity, the sustainability of such interventions is key^{47,48,49}. Moreover, although the short-term interventions may show promising results, the sustainability and impact of these strategies over extended periods remain unclear, highlighting the need for longitudinal studies to assess their efficacy⁵⁰. Understanding which interventions yield lasting benefits and how to maintain healthy behaviors in children over time is crucial for combating the obesity epidemic and reducing associated health risks.

⁴² Dhorajiwala, T., Thornton, W., Bose-Haider, B., & Puttha, R. (2010). *Scopes, limitations and satisfaction in managing childhood obesity in primary and secondary healthcare services' time for improvements.*

⁴³ Min, J., Goodale, H., Xue, H., Brey, R., & Wang, Y. (2021). *Racial-ethnic disparities in obesity and biological, behavioral, and sociocultural influences in the United States: a systematic review.* *Advances in Nutrition*, 12(4), 1137-1148.

⁴⁴ Rana, S., Sultana, A., & Bhatti, A. A. (2021). *Effect of interaction between obesity-promoting genetic variants and behavioral factors on the risk of obese phenotypes.* *Molecular Genetics and Genomics*, 296, 919-938.

⁴⁵ Barboza, J. J., Salvador-Oscco, E., Torres, P., & Rosero, D. R. (2023). *Factors related to the success of anti-obesity strategies: a scoping review.* *Frontiers in Endocrinology*, 14, 1259168.

⁴⁶ Lee, A., Cardel, M., & Donahoo, W. T. (2019). *Social and environmental factors influencing obesity.*

⁴⁷ Flynn, A. C., Suleiman, F., Windsor-Aubrey, H., Wolfe, I., O'Keeffe, M., Poston, L., & Dalrymple, K. V. (2022). *Preventing and treating childhood overweight and obesity in children up to 5 years old: A systematic review by intervention setting.* *Maternal & Child Nutrition*, 18(3), e13354.

⁴⁸ Flynn, A. C., Suleiman, F., Windsor-Aubrey, H., Wolfe, I., O'Keeffe, M., Poston, L., & Dalrymple, K. V. (2022). *Preventing and treating childhood overweight and obesity in children up to 5 years old: A systematic review by intervention setting.* *Maternal & Child Nutrition*, 18(3), e13354.

⁴⁹ World Health Organization. (2020). *Population-based approaches to childhood obesity prevention.* 2012. Geneva, Switzerland.

⁵⁰ Norman, Å., Zeebari, Z., Nyberg, G., & Elinder, L. S. (2019). *Parental support in promoting children's health behaviours and preventing overweight and obesity—a long-term follow-up of the cluster-randomised healthy school start study II trial.* *BMC pediatrics*, 19, 1-11.

6.2.3 Research Questions & Hypothesis

From the analysis of related research and the identified gaps, we formulated the following primary research question:

Q1: “What impact will the personalized recommendation for lifestyle modification have on awareness and adherence to healthy behaviors of children, adolescents, and families?”

The secondary research questions focus on identifying high-risk groups for metabolic dysfunction in obese children and adolescents and exploring how genes and lifestyle modifications can influence treatment effectiveness and health outcomes. We identified three secondary research questions:

Q2: “What are the similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications between patients with obesity (metabolically healthy and metabolically unhealthy) and healthy individuals (control), to define subsets (=clusters) of patients who are at the highest risk of metabolic dysfunction?”

Q3: “What is the impact of genetic predisposition and epigenetic modifications on the efficacy of behavior modification (i.e. physical activity and micro-moments)”?

Q4: “Can the use of the EU Childhood Obesity Platform and the risk assessment modules contribute to health outcomes and well-being of children and adolescents?”

6.2.4 Primary and Secondary Aims and Outcomes

6.2.4.1 Study Aims of Co-creation Workshops

- (1) To re-evaluate the Personas and refine user-requirements and stories based on feedback from real-world subjects.
- (2) To refine the digital interventions to ensure adherence and sustainability.
- (3) To refine the study to ensure minimal dropout and maximal output with minimal possible effort from the end-subjects.

6.2.4.2 Study Aims and Outcomes of the Intervention Study

Primary aims:

- 1) To evaluate the impact of genetic predisposition and epigenetic modifications on the efficacy of behavior modification.
- 2) To evaluate the acceptance and impact of BIO-STREAMS recommendation tools and micro-moment-based interventions for lifestyle modifications on awareness and engagement in preventive behaviors of children, adolescents, and families.

Secondary aims:

- 1) To identify similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications differentiating between **children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM) and children with overweight/obesity with metabolic abnormalities (COMA).**
- 2) To empower parents and children to prevent and/or treat obesity through new tools and services for informed decisions about lifestyle choices.
- 3) To evaluate the possible benefits of the recommendation tool towards health outcomes in children & adolescents by evaluating the improvement in health/food literacy, quality of life and well-being, increase of self-regulation and decrease in mental distress, including anxiety, depression, and self-perceived stigma
- 4) To analyze the impact of the personalized risk assessment on preventive behavior (i.e. following the recommendations) of children and families.
- 5) To quantify medical costs related to overweight/obesity management

6.2.4.3 Outcomes of the Intervention Study

Primary outcomes:

10. Number of new biological pathways conferring the efficacy of preventive behavior.
11. Acceptability and usability of the mobile application and interventions measured through affective attitude (user experience) and participant engagement, trust and acceptance, perceived burden of the behavior modifications and adherence.

The exact instruments to measure the outcomes listed above can be found in section 6.3.4.2.2.

Secondary outcomes:

- 1) Sensitivity and specificity of defining the subsets of patients at risk for metabolic dysfunction.
- 2) Reduction in body weight of 5% or centiles of BMI by 5 percentile points or z-score BMI change by 0,25, reduction in bodyfat, reduction in other anthropometric parameters.
- 3) Improvement of health/food literacy.
- 4) Improvement in quality of life.
- 5) Improvement in well-being.
- 6) Increase in self-regulation.
- 7) Decreased mental distress, including anxiety, depression, and self-perceived stigma.
- 8) Medical costs related to overweight/obesity management.

The exact instruments to measure the outcomes listed above can be found in section 6.3.4.2.2.

6.3 Study Design

Mixed methods study with a Within Subject Design

The main aim of this study is to design, evaluate and validate a personalized recommendation system for obesity prevention and management as a user-centered, ethically sound, and culturally sensitive digital solution. The study will extend the recommendation system, developed using retrospective cohorts collected during the BIO-STREAMS retrospective study (NKUA: EB-PASCH-MoM: 01/05/2024, Re: PASCH-EIΣ-5593-01/03/2024; BLOCKS: 19/01.06.2023; CHUL: 2024/82; KI: 2024-02377-01-585645; UKCM: UKC-MB-KME-17/24; VHIR: PR(AG)127/2024; PENTELI: 3271/14-3-2024) and will further enrich and explore similarities and differences in clinical presentation, personal exposome, genetic predisposition and epigenetic modifications differentiating between children without overweight/obesity (CWO), children with overweight/obesity with normal metabolic parameters (CONM) and children with overweight/obesity with metabolic abnormalities (COMA).

The study will be carried out in two parts, the **first study** will involve value-sensitive design and public-patient involvement through co-creation workshops to ensure: (1) interventions are tailored to address the unique needs and values of individual families, taking into account their cultural background, socioeconomic status, and lifestyle choices, (2) interventions are culturally appropriate, feasible, and sustainable and (3) high level of awareness about childhood obesity in the targeted piloting environments, empowering families and communities to make healthier choices and create healthier environments for their children. Two parts of a co-creation workshop will be carried out covering different topics. The **second study** will involve the validation of the digital solutions in a prospective study, where the user experience (engagement, acceptance, adherence) will be assessed, as well as the impact of the solution on targeted health outcomes. To this end, participants will then enter a 4-month intervention program supported by an internet-based application where individual-centric and family-centric recommendations, based on micro-moments, for physical activity and changes in dietary intake will be generated using the BIO-STREAMS EU Childhood Obesity Platform recommendation toolsets. At the end of the intervention participants will undergo a follow-up evaluation and the efficacy of the intervention will be explored through user experience (engagement, acceptance, adherence) and the improvements in participants' characteristics (e.g. health/food literacy, anthropometrics, quality of life, mental distress). In addition, biological (genetic and epigenetic) pathways conferring the success/efficacy of the intervention will be explored.

6.3.1 Sample Size Justification

6.3.1.1 Sample Size Justification for the Co-creation Workshops

The work carried out in the context of co-creation workshops involves dynamic and interactive workshops that are designed to be practical, engaging, and collaborative. These workshops aim to foster creativity, problem-solving skills, and active participation among participants. Related studies report on a moderate number of participants, ranging from 15 to 45 individuals, up to 8 individuals per session, including children and facilitators, to maintain a productive and inclusive



environment. The interventional study will take place in 6 different cultural environments, i.e. Slovenia, Spain, Greece, Sweden, Belgium and Bulgaria. We estimate a minimum of 144 participants in total, from different age groups (minimum 36 participants per age-group in total; (i) up to 8 years, (ii) 8-10 years, (iii) 10-14 years, (iv) 14-18 years) and cultural settings (minimum 24 participants per piloting county) to ensure effective engagement, collaboration, and diverse perspectives.

6.3.1.2 Sample Size Justification for the Intervention Study

To evaluate primary and secondary outcomes, the data will be analyzed using a statistical information management computer tool, e.g., SPSS, SAS or RStudio. To evaluate the impact of the platform and to measure primary outcomes, we hypothesize a small effect size ($f = .05$). The relevant related studies include behavioral interventions in the form of dietetic counselling, physical activities and/or lifestyle counselling (or a combination) and evaluate successfulness by measuring body weight change (e.g. body weight of 5% or centiles of BMI by 5 percentile points or z-score BMI change by 0,25), body fat reduction (e.g. change of body fat by at least 5%), anthropometry and blood pressure. The effect size of intervention within related studies is estimated at low, i.e. $.05$ and studies show that 5-10% reduction in weight can significantly improve the risks of premature death or developing comorbidities.

To estimate statistically relevant sample size, we carried out power calculations using the G*Power software. Patient-related analyses will predominantly be based on the ANOVA repeated measures statistical test with the within-between interaction (3 groups, 2 measurements). As we hypothesize a small effect size ($f = .05$) and intend to use a conventional significance threshold and power ($\alpha = .05$, $1-\beta = .80$), the total sample size needed to detect the effects is 969 participants in total (i.e., 323 in the CONM group, 323 in the COMA group and 323 in CWO group). Since we foresee 8-10% dropout we will recruit 1050 participants in total (350 per group). Secondary sensitivity analyses according to specific characteristics e.g. weight status, SES, Age etc. will be conducted under secondary aim.

Power calculation

By convention, maximum acceptable value for β in bio-statistical literature is $.20$ or a 20% chance that null hypothesis is falsely accepted. Usually, most clinical trials use the power ($1-\beta$) of 80%. Since the pilot studies are exploratory in nature, we set the power at 80%. The false positive rate α , as it is conventional and used in most studies, is set at 5%.

Table 4: Subject distribution per cohort and pilot site (intervention study)

Partner	Country	CWO to be recruited (target)	CONM to be recruited (target)	COMA to be recruited (target)

University Clinical Centre Maribor	Slovenia	50	50	50
National and Kapodistrian University of Athens	Greece	50	50	50
Karolinska Institute	Sweden	50	50	50
Blocks Health and Social Care EOOD	Bulgaria	50	50	50
Hospital Universitari Vall d'Hebron	Spain	50	50	50
Centre Hospitalier Universitaire de Liège	Belgium	50	50	50
Penteli General Children's Hospital	Greece	50	50	50

6.3.2 Study Population

6.3.2.1 Study Population for the Co-creation Workshops

The same children will be allowed to participate in both parts of the co-creation workshop. They will be recruited through clinical sites that take part in the study.

144 participants in total (pilot sites altogether) will participate, from different age groups (36 participants per age-group in total; (i) up to 8 years, (ii) 8-10 years, (iii) 10-14 years, (iv) 14 -18 years) and cultural settings (24 participants per piloting county) to ensure effective engagement, collaboration, and diverse perspectives. 48 CWO, 48 CONM and 48 COMA will be included in the co-creation workshops during the first part of the study.

Piloting countries

1. Slovenia (University Medical Centre Maribor; UKCM)
2. Greece (National and Kapodistrian University of Athens; NKUA and Penteli General Children's Hospital; PENTELI)
3. Sweden (Karolinska Institute; KI)
4. Bulgaria (Blocks Health and Social Care EOOD; BLOCKS)
5. Spain (Hospital Universitari Vall d'Hebron; VHIR)
6. Belgium (Centre Hospitalier Universitaire de Liège; CHUL)

Table 5: Subject distribution per cohort and piloting country (co-creation workshops)

	Slovenia	Greece	Sweden	Bulgaria	Spain	Belgium	Total (min)
<8	6-8	6-8	6-8	6-8	6-8	6-8	36
8-10	6-8	6-8	6-8	6-8	6-8	6-8	36
10-14	6-8	6-8	6-8	6-8	6-8	6-8	36
14-18	6-8	6-8	6-8	6-8	6-8	6-8	36
Total (min)	24	24	24	24	24	24	144

Inclusion Criteria

1. Ability to give a signed informed consent (by participants or parents/legal guardians, depending on the local legal requirements)
2. Age: 5-18 years

Exclusion Criteria

1. Inability to give informed consent and/or assent (e.g., in case of intellectual disability)

6.3.2.2 Study Population for the Intervention study

The intervention will include 350 children without overweight/obesity (CWO), 350 children with overweight/obesity with normal metabolic parameters (CONM) and 350 children with overweight/obesity with metabolic abnormalities (COMA), from 7 clinical sites to account for the minimum sample size per group (see section 6.3.1.2).

Pilot sites

1. University Medical Centre Maribor (UKCM)
2. National and Kapodistrian University of Athens (NKUA)
3. Karolinska Institute (KI)
4. Blocks Health and Social Care EOOD (BLOCKS)
5. Hospital Universitari Vall d’Hebron (VHIR)
6. Centre Hospitalier Universitaire de Liège (CHUL)
7. Penteli General Childrens’ Hospital (PENTELI)

Recruitment



CONM and COMA groups will be recruited within the pilot sites, where patients visiting the clinics will be added to a list of possible participants. They will also be screened for the inclusion criteria listed below and assigned to the appropriate group (CONM or COMA). We will anonymize personal data of the participants that will meet the inclusion criteria before including them in the study.

CWO group will be recruited by different means in different piloting sites due to differences in accessibility of individuals without obesity or overweight. Most of the sites will be able to recruit via the clinics or primary care, whereas piloting sites that do not have such possibility will recruit siblings of their patients, children at vaccination visits or emergency visits. Potential participants will have to meet the following inclusion criterion:

- Patient is not treated for a condition that could influence their metabolic status (e.g. eating disorders, diabetes, ...)
- Patient does not have a diagnosis of clinical condition that requires a specific diet (e.g. coeliac disease, allergies,...)

Sex distribution: In 2020, around 175 million children and adolescents aged 5-19 years worldwide were considered obese⁵¹. In the study, we will strive towards recruiting equal proportion of female and male subjects. However, it must be noted that boys are more susceptible to obesity than girls. A significant difference between genders in European cohorts was in favor of girls, i.e. fewer girls were obese than boys. On average across 23 EU countries, 14% of boys and 10% of girls aged 7-8 years old were obese, according to the COSI study⁵². Overall, the prevalence of overweight and obesity among boys is 31%, while among girls it is 28%⁵³. Thus, a somewhat larger proportion of boys in the sample is acceptable.

It should be noted that the piloting sites are not involved in participant recruitment in any other study.

Inclusion Criteria

- Ability to give informed consent
- Owning a smartphone or tablet (available in the home environment, not necessarily personal device of the participant) OR parent owning a smartphone (for younger children)
- Age: 5-18 years old

⁵¹ <https://www.statista.com/statistics/1386146/number-of-obese-children-and-adolescents-worldwide-forecasts-by-gender/>

⁵² https://www.oecd-ilibrary.org/sites/health_glance_eur-2018-26-en/index.html?itemId=/content/component/health_glance_eur-2018-26-en

⁵³ <https://www.who.int/europe/news/item/03-03-2023-childhood-obesity--five-facts-about-the-who-european-region>

- For age group of 5-12⁵⁴ years old, parents will need to be involved together with the children

Inclusion into groups

For our study aims, children with overweight or obesity will be recruited based on criteria below:

- Overweight: BMI more than 1 SD to 2 SD above the median of the WHO growth reference for children adolescent
- Obesity: BMI more than 2 SD above the median of the WHO growth reference for children and adolescent

Further, we will stratify the group with children with overweight or obesity into two groups based on IDF⁵⁵ criteria (see table below):

- **Children with overweight/obesity with normal metabolic parameters (CONM)**
- **Children with overweight/obesity with metabolic abnormalities (COMA)**

For children under 16 years old, one criterion needs to be fulfilled to classify for COMA group, for children 16 and above, two criteria need to apply. The third, the control group, will consist of children also recruited in a clinical setting, but with normal weight:

- **Children without overweight/obesity:** BMI up to 1 SD above the median of the WHO growth reference for children and adolescent⁵⁶

Table 6: The IDF definition of metabolic parameters in children and adolescents

Age group	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Glucose
6-<10*	≥90 th percentile				

⁵⁴ According to Piaget’s theory, after 11 years of age children start to develop the ability of abstract and deductive thinking. Ahmad, S., Ch, A. H., Batool, A., Sittar, K., & Malik, M. (2016). Play and Cognitive Development: Formal Operational Perspective of Piaget's Theory. Journal of Education and Practice, 7(28), 72-79.

⁵⁵ <https://pubmed.ncbi.nlm.nih.gov/17850473/>

⁵⁶ WHO growth reference for children and adolescent: <https://www.who.int/tools/growth-reference-data-for-5to19-years>

10– <16	≥90 th percentile or adult cut-off if lower	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic BP ≥130 or diastolic BP ≥85 mm Hg	FPG ≥5.6 mmol/L (100 mg/dL)** or known T2DM
16+(A dult criteria)	WC ≥ 94cm for Europid males and ≥ 80cm for Europid females, with ethnic- specific values for other groups)	≥1.7 mmol/L (≥150 mg/dL) or specific treatment for high triglycerides	<1.03mmol/L (<40 mg/dL) in males and <1.29mmol/L (<50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥5.6 mmol/L (100 mg/dL) or known T2DM

Notes. BP: blood pressure; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; IDF, International Diabetes Federation; T2DM, type 2 diabetes mellitus; WC, waist circumference.

* Metabolic syndrome cannot be diagnosed

Exclusion Criteria

- Age under 5 or above 18 years old
- Severe mental disorder (schizophrenia, bipolar disorder, severe depressive disorder)
- Inability to give informed consent and/or assent (e.g., in case of intellectual disability), by parents or children (age depending on the local legislation)
- Severe cognitive disorder that would prevent to follow-up on recommendations, and epileptic disorders
- Children with severe chronic medical conditions
- Orthopedic affection limiting physical activity
- Use of medication known to effect body weight
- Known family issues that would affect general compliance and attendance at follow-up visits
- Diagnosis of clinical condition that requires a specific diet (e.g. coeliac disease, allergies, etc)
- BMI lower than 2 SD below the median of the WHO growth reference for children and adolescents

6.3.3 Timing of the Study Procedures

6.3.3.1 Timing of Study Procedures for Co-creation Workshops

The foreseen schedule for the co-creation activities was 4 months. We started with the preparatory activities and recruitment, after receiving the ethics approval. The detailed schedule is listed below (M refers to the month of the study, not the month of the project):

- M01 (October 2024) – ethics approval for the study received recruitment for co-creation workshops can begin.
- M02 (November 2024) – M04 (January 2025) – a series of co-creation workshops organized at pilot sites. At least 1 workshop per age group.
- M05 (February 2025) – M06 (March 2025) – thematic analysis of the results and refinement of the interventional study protocol.
- M07 (April 2025) – M08 (May 2025) – all studies updated, and all modifications mediated with the relevant ethics committees, the interventional study can begin.

6.3.3.2 Timing of Study Procedures for the Intervention Study

The foreseen duration for the interventional study is 7 months per inclusion. The first 2 months are foreseen for the baseline assessment and training. Then, a 4-month intervention will begin, the first part will be an active intervention lasting 1 month and the second part an unsupervised active intervention that will be carried out for 3 months. In the supervised intervention participants will be monitored and contacted in case issues are detected and in the unsupervised intervention no such monitoring is conducted. The final follow-up will be carried out 1 month after the end of 4-month period of active intervention. The detailed schedule is defined as follows:

1. May 2025 (M01):

- All the co-creation activities and patient-public-involvement activities have been carried out
- The study protocol is finalized and reflects the values and perspective of the real-world subjects representing participant Personas of the study.
- All sites have submitted amendments to the relevant ethics committee

2. May 2025 (M01) to August 2025 (M04):

- All relevant DTA/DPAs are signed and come into force.
- The study had been presented to possible subjects, at least 500 subjects per pilot site
- At least 40 subjects per partner site have committed to participate
- All sites receive confirmation related to the amendments that were the result of the co-creation activities and patient-public-involvement activities

3. August 2025 (M04) to February 2027 (M23):

- Execution of the study and progressive inclusion of participants, each participant starts with the study immediately after they are recruited
- The last participant enters the study in July 2026
- The last participant finishes with the study in February 2027

4. February 2027 (M23) to April 2027 (M25):

- Analysis of the results
- Presentation of the results to the subjects in the form of workshops

6.3.4 Description of Study Procedures

6.3.4.1 Description of Study Procedure for Co-creation Workshops

Two parts of a co-creation workshop will be carried out by each of the six piloting countries. The following key activities will be executed to achieve the aim of designing and evaluating a user-centered, ethically sound, and culturally sensitive personalized intervention system for obesity prevention and management:

- **Introduction and context setting:** Use of storytelling, videos, and interactive presentations to provide an engaging introduction to the project and its goals. We will emphasize the importance of children and adolescents' voices in shaping interventions that meet their needs.
- **Ideation and brainstorming:** We will facilitate creative and interactive sessions to generate ideas and concepts for the intervention system. Techniques such as drawing, role-playing, or group discussions will be facilitated to encourage participation and expression of ideas.
- **Data collection:** Use of child-friendly methods such as drawings, stories, or games to capture participant contributions and feedback during the workshops.
- **Stakeholder engagement:** We will share the workshop outcomes with relevant stakeholders, including educators, healthcare professionals, and policymakers, to ensure that children and adolescents' voices are heard in the design and implementation of obesity prevention interventions.
- **Intervention refinement:** Use of the insights gathered from the workshops to refine and finalize the design of the intervention system, ensuring that it reflects the preferences and needs of the target audience. This includes child-friendly evaluation methods to assess the effectiveness and acceptability of the intervention system, involving children and adolescents in the evaluation process.

To facilitate effective feedback, the BIO-STREAMS Consortium will create a supportive environment where children and adolescents will feel comfortable sharing their feedback on the prototypes. Simple language and visuals will be used to capture their input and ideas for improvement. Discussions on ethical and cultural considerations will be integrated and carried out in a way that is accessible and relatable to children and adolescents. We will use real-life

examples and storytelling to illustrate key concepts. For lower age groups, the timing and execution of the workshops will be adjusted depending on the actual age distribution of the participants.

The workshop will be carried out in two parts, each will last approximately 1 hour and 30 minutes.

Part 1: Persona Evaluation and User Requirements Assessment and Study Design

(1) Persona Evaluation and User Requirements Assessment (30 minutes)

Introduction to Personas (5 minutes): The session will begin by explaining the concept of personas and user requirements in a simple and relatable manner. We will use narrative story boards, as posters or character cards to illustrate the personas developed by the BIO-STREAMS experts in an engaging format (see Appendix 1: Child Persona Description). We will encourage children to examine each persona and discuss its qualities and characteristics.

Group Discussion (10 minutes): We will facilitate a group discussion where children will evaluate the quality and relevance of the personas with the help of predefined questions (see Appendix 2: Questions for Input on Child Persona). They will be prompted to consider whether the personas accurately reflect the diversity of potential users and their needs.

Introduction to User Requirements (5 minutes): We will introduce the concept of user requirements and present a list of questions to collect them (see Appendix 3: Questions for Input on User Requirements, Study Design and Intervention). We will ask children whether they find the questions 1) understandable and 2) important. The refined list of questions will be used in Part 2, to elicit actual user-requirements for BIO-STREAMS.

Group Discussion (10 minutes): We will facilitate a group discussion where children will discuss and answer the relevant questions on the BIO-STREAMS digital solution.

(2) Study Design (35 minutes):

We will continue the workshops with the session on study design. In the session, we will focus on child-friendly evaluation methods to assess the effectiveness and acceptability of the intervention system. The goal is to refine the clinical study and evaluate which and how many instruments should be used to assess the study outcomes, the effort children are willing to put into it and how often. The key activities will include:

Introduction to Study Design (5 minutes): We will explain the concept of a study design and its importance in evaluating the BIO-STREAMS solution. We will use simple language and visuals to illustrate key concepts such as study objectives, methods, and outcomes.

Group Activity (25 minutes): Children will be divided into 3 small groups and provided with scenarios and questions (see Appendix 3: Questions for Input on User Requirements, Study Design and Intervention) related to study design. We will ask them to brainstorm ideas related to recruitment, daily activities carried out, questions to be asked, effort to be dedicated to the study per day, etc.



Presentation and Discussion (15 minutes): Each group will be invited to present their ideas and discuss them with the wider group. Facilitate a conversation about the benefits and challenges of the activities and the study design, encouraging children to share their perspectives and insights.

Part 2: Mockups, Demos, and Digital Solutions (1 hour 30 minutes)

In the second series of workshops, we will evaluate user experience, motivation, effort and willingness of participants while showing them mockups and demos of the BIO-STREAMS digital solutions.

Introduction to Mockups and Demos (10 minutes): We will explain what mockups and demos are and how they can help visualize digital solutions. We will show examples of mockups or prototypes in a format that is easy for children to understand.

Interactive Demonstration (30 minutes): We will provide interactive demonstrations of digital solutions or interventions of BIO-STREAMS, using simple prototypes, mockups, and interactive tools (see Appendices 5 and 6). We will try to allow children to explore and interact with the prototypes, encouraging them to provide feedback and suggestions for improvement.

Group Discussion (30 minutes): We will facilitate a discussion about the digital solutions and interventions, focusing on their usability, functionality, and relevance to children in different age groups. We will encourage children to share their thoughts, ideas, and preferences. During the sessions, children will respond to a series of questions (see Appendix 3: Questions for Input on User Requirements, Study Design and Intervention) to express different user requirements related to BIO-STREAMS in their own language.

Post-workshop Activities

The BIO-STREAMS consortium will share the workshop outcomes with relevant stakeholders, including educators, healthcare professionals, and policymakers, to ensure that children and adolescents' voices are heard in the design and implementation of obesity prevention interventions. The insights gathered from the workshops will be used to refine and finalize the design of the intervention system and the intervention study, ensuring that it reflects the preferences and needs of the target audience.

The study design will include child-friendly evaluation methods to assess the effectiveness and acceptability of the intervention system, involving children and adolescents in the evaluation process.

The BIO-STREAMS consortium will share the outcomes of the workshops and the finalized intervention design with the wider community through child-friendly formats such as videos, comics, and interactive websites, to raise awareness and promote engagement.

6.3.4.2 Description of Study Procedure for the Intervention Study

6.3.4.2.1 Overview

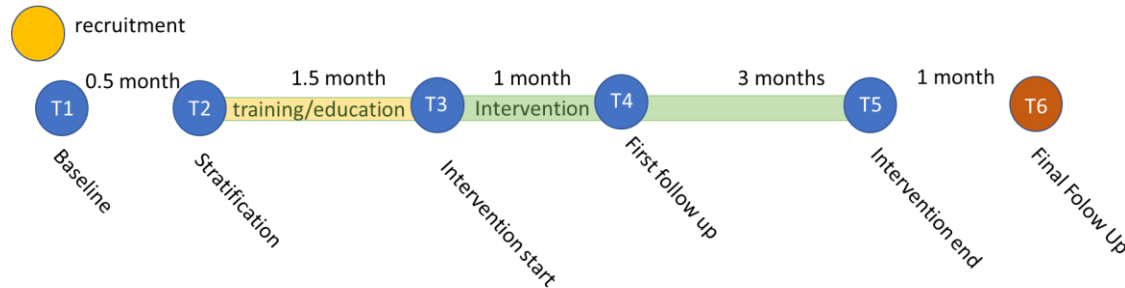


Figure 5: Intervention study data collection timeline

Each participant will participate in the study for 6 months with the final follow-up questionnaire 1 month after the study ends. In each of the seven sites, potentially eligible participants will be approached and recruited for the study. In total, there are five data collection points (no data collection in T2), two of which will be in-person visits to the pilot sites to collect anthropometric measurements and biosamples. In T1 and T6, psychological measurements will be collected in paper-pencil format.

6.3.4.2.2 Data Collection Procedures per Time Point

Before entering the study, potential participants will undergo eligibility screening regarding inclusion and exclusion criteria, which is described in section 6.3.2. Already at this point, researchers will be mindful of recruiting participants from each study cohort (CWO, CONM, and COMA), while checking the eligibility criteria of potential participants.

After enrolment and before the start of the interventions, baseline data will be collected (T1; see overview of measures in Table 4). We will collect information regarding lifestyle (dietary habits and physical activity), health literacy, family and psychological data (for specific questionnaires, see Table 5) through validated questionnaires and data related to socioeconomics. We will also collect anthropometric parameters (height, weight, BMI, and waist circumference). Finally, we will collect saliva from all three participant groups (CWO, CONM, COMA) to extract genetic and epigenetic markers.

Based on anthropometric parameters and biochemical markers children and adolescents will be stratified into 3 groups (T2), CWO, CONM, and COMA (please review section 6.3.2.2. for more details). To extract biochemical parameters (glucose, blood pressure, triglycerides, HDL-C) we will use existing laboratory analysis from all groups which must not be older than 1 year. For CONM and COMA groups, if no existing data is available, blood samples will be taken from participants. After stratification, recruited subjects will undergo training and educational activities.

The data will be fed to the BIO-STREAMS Recommendation Engine that will return recommendations for behavior modification as part of the supervised intervention starting in **T3**. The recommendations provided regarding physical activity and nutrition will be reviewed by the clinicians in charge of the clinical site. The initial recommendations will be generated by a machine model (decision tree), based on the existing guidelines. During intervention, all the participants, including the healthy cohort, will receive standard care. Additionally, they will be given self-management recommendations based on BIO-STREAMS tools by the consulting clinicians related to diet and physical activity, which will be instructed to follow for 4 weeks. This will be done in addition to regular clinical pathways/routine. Individuals will also be asked to fill in a diary assessment between time points T3 and T5 (using mobile app) documenting, e.g., what recommendations they follow, diary patterns and food intake, and activity.

Participants' baseline data will also be fed to the risk assessment tool to receive information on their overall risk of adverse metabolic effects to promote preventive behavior of children and families, motivate them towards behavioral change and improve adherence to lifestyle interventions.

After 1 month, participants will fill in questionnaires related to user experience, usability, acceptance, and trust and data on adherence to the lifestyle recommendations given by the BIO-STREAMS recommendation tool and participant engagement will be collected through the app (**T4**). This will allow us to evaluate the efficacy of interventions. Where necessary, the interventions will be adjusted to better fit the context of the individuals. Subjects will be asked to follow the modified unsupervised interventions for a further 3 months. Individual consultations will be available following participants' request and in case the consortium detects low engagement in the digital intervention.

After 3 months, participants will once again answer questionnaires on user experience, usability, acceptance, trust, and perceived research burden, data on adherence to the lifestyle recommendations and participant engagement will be once again collected (**T5**).

At **T6** saliva will be collected from all participant groups (CWO, CONM, COMA) to carry out the epigenetic analysis; using this data we will evaluate the impact of genetic-predisposition epigenetic modification (compared between T1 and T6) on the efficacy of interventions. T6 has been chosen for saliva collection to ensure enough time for epigenetic changes to occur. The final set of questionnaires will be administered, including psychological measures (see Table 4), and anthropometric measures (height, weight, waist circumference). Adherence and participant engagement will be measured for the last time through the app. At the end of the project a series of workshops will be organized to disseminate the findings and results of the study to the participants and the wider public. On the same date, clinicians will present and comment on each individual results the participants achieved during the study.



Table 7 : A list of all collected measurements in the Intervention Study

Outcome by type	Method of collection	Time point
Demographic data		
Participant age	Varies	T1
Family socioeconomic status	Varies	T1
Biomedical measures		
Height	In-person measurement	T1, T6
Weight	In-person measurement	T1, T6
Waist circumference	In-person measurement	T1, T6
Blood pressure	Retrospective blood records*	T1
Glucose	Retrospective blood records*	T1
Tryglicerides	Retrospective blood records*	T1
HDL-C	Retrospective blood records*	T1
Saliva – genetic marker	In-person buccal sampling	T1, T6
Saliva – epigenetic marker	In-person buccal sampling	T1, T6
Dietary habits	Self-report questionnaire in digital form	T1, T3, T4, T5
Physical habits	Self-report questionnaire in digital form	T1, T3, T4, T5
Psychological measures		
Anxiety	Self-report questionnaire	See Table 5
Depression	Self-report questionnaire	See Table 5
Self-perceived stigma	Self-report questionnaire	See Table 5
Self-regulation (exercise)	Self-report questionnaire	See Table 5
Self-regulation (eating behavior)	Self-report questionnaire	See Table 5
Well-being	Self-report questionnaire	See Table 5
Quality of life	Self-report questionnaire	See Table 5
Health/food literacy	Self-report questionnaire	See Table 5

Response to intervention measures		
User experience	Self-report questionnaire in digital form	See Table 5
Acceptance + Trust	Self-report questionnaire in digital form	See Table 5
Usability	Self-report questionnaire in digital form	See Table 5
Adherence	Through the ActiveHealth app	See Table 5
Participant engagement	Through the ActiveHealth app	See Table 5
Perceived burden	Self-report questionnaire	See Table 5
Costs		
Medical costs	Self-report questionnaire	

*For CONM and COMA groups, if retrospective blood records are not available, blood sample will be extracted from participants.

Table 8: Detailed overview of self-report questionnaires, number of items, and time points of collection

Outcome	Instrument	Number of self-report items	T1	T3	T4
Anxiety	PSWQ-C (Penn State Worry Questionnaire for Children)	14	x		
Depression	CES-DC (Center for Epidemiological Studies Depression Scale for Children)	4	x		
Self-perceived stigma	WSSQ (Weight Self-Stigma Questionnaire)	12	x		
Self-regulation	SRQ (Self-regulation questionnaire) - exercise dimension, SREBQ (Self-regulation of eating behavior questionnaire)	12 and 5	x		
Well-being	WHO-5 (Child Well-being Index)	5	x		
Quality of life	KIDSCREEN-10	10	x		
Health/food literacy	FNLIT (Food and Nutrition Literacy)	15	x		

Dietary habits	Regular questionnaire used in clinics*	A couple of items per day	x	x	
Physical activity	Regular questionnaire used in clinics*	A couple of items per day	x	x	
User experience	UEQ-S (User Experience Questionnaire Short Version)*	8			
Acceptance + Trust	UTAUT2*	12			
Usability	SUS (System Usability Scale)*	13			
Adherence	E.g. nr. responses, frequency of responses, nr. entries, following recommendations (through micro-moments), ...	/			
Participant engagement	Measured through the app with common analytics	/			
Perceived burden	PeRBA (Perceived Research Burden Assessment)*	7			
Number of self-report items per time point			77	0	

Note. * - Questionnaires will be administered in a digital form through the ActiveHealth app

6.3.4.2.3 Medical Cost Data Collection

Economic data related to direct medical costs of overweight/obesity management will be collected starting from administrative data of the clinical sites participating in the study. In detail, all healthcare services (i.e. hospitalizations, outpatient activities, drugs and emergency department visits) provided to each subject enrolled in the study that are considered as related to obesity/overweight by the physician managing the clinical pathway will be reported within a case report form (i.e. considering the type of service; the date or month in which the service is provided; the duration of the service, in case of hospitalization; the posology in case of drugs prescription; the reason for the service prescription and delivery). The cost of each service will be quantified considering the related reimbursement tariffs, being consistent with the perspective adopted in the analysis, which is that of the National Health Service / payer.

At a hospital level, information related to healthcare services provided by different providers to the subjects enrolled could be missing. Thus, the data collected will be integrated by a questionnaire to be filled by the physician in charge of the patient pathway, with information provided by caregivers or patients related to the healthcare services (overweight/obesity related) received by the patient from the enrollment to the follow-up visit. Most healthcare services related to overweight/obesity are expected to be provided by the clinical site participating in the study. Therefore, the data collected through caregivers and patients self-report (which have a lower reliability compared with data collected through medical records) are expected to be residual. This element, along with the physicians' experience in assessing the level of reliability of self-reported data, will grant the representativeness of the direct medical costs related to overweight/obesity management during the study period. The exact process will be aligned with relevant stakeholders during the co-creation workshops.

6.3.4.2.4 Saliva Collection and Genetic Analysis

Saliva samples will be collected using buccal brushes. The process includes the collection of cells from saliva and cheek allowing a non-invasive and simple method of obtaining bio-samples with quality for DNA extraction. Two properly sterilized DNA-free brushes contained in plastic pouches will be provided for each participant. Handling from the extremity opposing the cheek swab, the collector will rub moderately the inside of the cheek of the participant for approximately one minute. Brush will be collected immediately inside the plastic pouch, whose microporous membrane will dry the sample and stabilize the DNA protecting it, even upon storage at room temperature. Pouches will be closed and a sticker containing an individual barcode will be attached. The process will be repeated for the second swab. The person responsible for the collection will write down the barcodes corresponding to each participant. Samples will be anonymized for the posting and for the EonGenetics laboratory. Upon arrival in the EonGenetics facilities, DNA samples will be immediately extracted using standardized methods. DNA extracts will be measured for DNA concentration using a Qubit Fluorometer that provides a high degree of accuracy. Samples will be stored at -80°C until their use.

For the detection of epigenetic biomarkers, we will use reduced representation bisulfite sequencing which covers over 80% of CpG sites and most gene promoters. This will be performed on the different groups of samples through a pooled analysis. Furthermore, subset of promising

epigenetic markers with relevance for BMI variation will be individually tested in each sample through the design of a targeted panel of methylation sites. We plan 2 months for the analysis.

Samples will be analyzed using two approaches that are complementary in several aspects:

- Detection of epigenetic biomarkers within overall groups. For that we will employ a pooled analysis that allows the analysis of DNA methylation across multiple samples in a cost-effective and efficient manner. Samples of each group (CWO, CONM, COMA) in each recruitment site will be carefully measured for DNA concentration and pooled into a single sample that corresponds to equal concentration of DNA of each sample in the analysis. Following that, samples will undergo the regular reduced representation bisulfite sequencing (RRBS) approach that includes DNA digestion, fragment size selection, bisulfite conversion and sequencing. Contrarily to the regular analysis of individual samples, pooled samples will be sequenced at high depth, allowing the generation of millions of reads that include the combined methylation profile of all the samples included. The existence of a large number of reads per region will allow us to obtain statistical significance. Statistical comparisons can be made between groups in the same recruitment sites, but more essential differences observed before and after the intervention period for the same group, allowing the identification of novel methylation biomarkers. The representativeness of the analysis will also be evaluated for specific methylation sites analyzed individually as described below.

- Samples will be individually tested for a set of CpG methylation sites already described in the literature, following our systematic review, but also from the preliminary results of our pooled analysis, as described. We will design primers specific to the bisulfite-converted DNA regions and evaluate the percentage of methylation using Illumina sequencing to obtain high coverage of the bisulfite-converted PCR products. Methylated sites are converted into uracil upon the treatment with sodium bisulfite that will show up as thymine in the sequencing products. Comparison of reads containing thymine or cytosine allows to establish rates of methylation per site. Sites analyzed individually per group will also be compared with the results for the pooled group for further validation of the methodologies. While the first approach aimed at detecting methylation biomarkers, this second one will provide individual profiles that can be integrated within the evaluation platform.

6.3.5 Data Analysis

6.3.5.1 Data Analysis for the Intervention Study Data

Given the comprehensive nature of the study, a multi-faceted data analysis approach will be necessary to appropriately analyze and interpret the data collected. The following table summarizes the initial analysis targeted.

Table 9: Summary of targeted initial analyses

Descriptive Analysis

Baseline Characteristics	Summarize the demographic, lifestyle, family, psychological, socioeconomic, and anthropometric/physiological parameters at baseline (T1). Use means, medians, standard deviations, and ranges for continuous variables; frequencies and percentages for categorical variables.
Follow-Up Data	Descriptive statistics to summarize adherence to interventions, changes in lifestyle, physical activity, and dietary patterns.
Economic data	Statistical analysis of economic variables will be limited to descriptive statistics. Data will generally be presented as mean (standard deviation) or median (range) and analysis of continuous variables with outliers represented by measures that are less likely to be affected by outliers (median, interquartile range [IQR]).
Comparative Analysis	
Pre- and Post-Intervention Comparisons	Use paired t-tests or Wilcoxon signed-rank tests for continuous variables (e.g., BMI, waist circumference, blood pressure) and McNemar's test for categorical variables to compare baseline (T1) and follow-up (T4 and T5) data.
Between-Group Comparisons	ANOVA or Kruskal-Wallis tests to compare changes across the three stratified groups (CWO, CONM, COMA). Post-hoc tests (Tukey or Dunn's test) to identify specific group differences.
Regression Analysis	
Impact of Interventions	Use linear or logistic regression models to evaluate the impact of interventions on outcome variables (e.g., BMI, biochemical parameters). Include baseline values and potential confounders (e.g., age, gender, socioeconomic status) as covariates.
Predictive Modeling	Develop models to predict the efficacy of interventions based on baseline characteristics, genetic, and epigenetic markers. Consider using multiple regression, LASSO regression, or machine learning techniques like random forests or gradient boosting.
Longitudinal Analysis	
Repeated Measures ANOVA or Mixed-Effects Models	Analyze the data collected at multiple time points (T1, T4, T5) to assess changes over time within subjects and between groups. Mixed-effects models can account for the within-subject correlation and handle missing data more effectively.

Behavioral Pattern	Perform cluster analysis on daily diary assessments to identify patterns or clusters in dietary and physical activity behaviors. This can help to tailor future interventions more effectively.
Epigenetic Patterns	Perform cluster analysis on genetic and epigenetic data to identify distinct profiles within and between groups. Use multivariate analysis techniques (e.g., canonical correlation analysis) to explore relationships between clinical presentation, exposome, genetic, and epigenetic data.
Qualitative Analysis	
Acceptance and Perception	Perform thematic analysis on qualitative data from questionnaires about the acceptance of the recommendation tool. Conduct content analysis on open-ended responses regarding engagement in preventive behaviors.
	Perform thematic analysis on qualitative data from follow-up interviews regarding perceived improvements in quality of life and well-being, and reductions in mental distress.

6.3.5.2 Data Analysis for Co-creation Workshop Data

Thematic Analysis and Outcome Generation

We will adapt thematic analysis techniques to analyze the workshop data, focusing on key themes related to children and adolescents' preferences, needs, and perspectives on obesity prevention and management interventions. The findings of the thematic analysis will be translated into actionable outcomes that prioritize the development of a user-centered, culturally sensitive interventions system tailored to the needs of children and adolescents. A public summary report of the workshop outcomes will be prepared and published via social media and BIO-STREAMS web page, using language and visuals that are accessible and engaging for children and adolescents, highlighting their contributions and recommendations.

6.4 BIO-STREAMS Technological Components

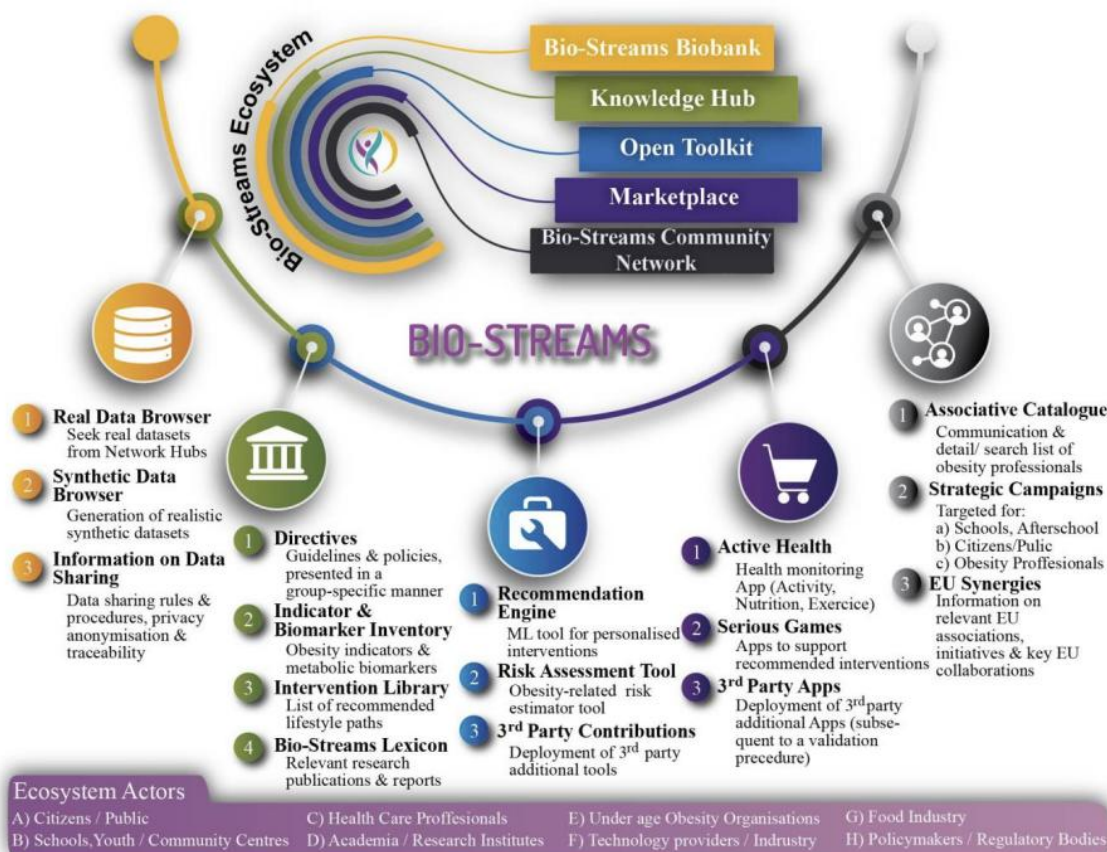


Figure 6: BIO-STREAMS technological components

BIO-STREAMS Ecosystem (Figure 6), includes 5 primary components supported by the necessary backbone services & packages. The BIO-STREAMS Biobank is at the heart of the ecosystem, with its decentralized architecture based on a Hub Network with local installations of the BIO-STREAMS Node Bundle, ensuring secure and interoperable data management across providers via the BIO-STREAMS Information Management System (IMS) and the Security Assurance Framework (SAF). Services include data audit, pseudonymization, anonymization and harmonization, along with the ML-assisted Synthetic Data Generator (SDG) used for anonymized data provision and algorithm training/testing. The Knowledge Hub will gather data on indicators and prognostic biomarkers (BIO-STREAMS Inventory), published research (BIO-STREAMS Lexicon), guidelines & interventions (BIO-STREAMS Directives & Intervention Library), while the BIO-STREAMS Open Toolkit is exploiting knowledge to implement personalized risk assessment workflows and design of recommended lifestyle pathways, utilizing back-end ML. In addition, the BIO-STREAMS Marketplace will provide a dedicated mobile app (ActiveHealth App) granting access to BIO-STREAMS services and facilitating interventions through serious games, while the

BIO-STREAMS Community Network will bring together relevant actors, enabling a) research and innovation on health & social sectors, b) community campaigns & stakeholder-engaging initiatives and c) community access to specialists via the BIO-STREAMS Associative Catalogue. Deployment will be aided by a dedicated clinical protocol.

6.4.1 BIO-STREAMS Federated Biobank: A Collection of Node Bundles

The BIO-STREAMS Biobank aims to adeptly navigate the challenges often faced by centralized biobanks, like the hurdles in achieving EU-wide integration, the integration of diverse datasets, and the complex issues surrounding data ownership. This innovative approach is made possible through a decentralized structure that transforms each participant into an independent hub, known as the BIO-STREAMS Biobank Hub. These hubs store pseudonymized and standardized datasets locally, maintaining privacy and uniformity across the network. Together, they create a unified Network that defines the BIO-STREAMS Biobank.

Clinical partners within BIO-STREAMS will each set up their BIO-STREAMS Node Bundle (BNB), comprising all necessary infrastructure to ensure data privacy and efficient network integration. The BNB acts as the cornerstone of this federated system, enabling each Hub to keep data under their own management, instead of centralizing all data into one main repository, while also facilitating a streamlined exchange and alignment of data between Hubs. The BNB's role is pivotal in maintaining the integrity and operational efficiency of the network. It ensures that each Hub can autonomously manage and control its own data while still participating in the larger biobanking initiative. The federated model enhances data security, improves scalability, and maintains compliance with local data governance regulations. Through the BNB, Hubs can share harmonized and pseudonymized datasets, contributing to a cohesive yet distributed network that supports collaborative research without compromising data autonomy.

The BNB includes the necessary computer resources for deployment and connection within the network of Hubs. Its data schema will be based on the structured description of overweight/obesity, resulting in a standardized data model that will derive from the work of Work Package 2 and Work Package 3, with related database services and regulatory protocols. Tools for data harmonization, curation and pseudonymization will be part of the integration. Communication with the IMS and the Authentication and Authorization Server will be established through associated Application Programming Interfaces (APIs). As the BIO-STREAMS solution progresses toward its full implementation, the BNB will be distributed to all networked Hubs for setup and interconnection with the BIO-STREAMS Obesity Platform via the APIs. The BNB will be installed in a server on the hospital premises.

6.4.2 BIO-STREAMS Information Management System

The Information Management System (IMS) is a software component designed to manage and govern access to clinical data from various sources. The system ensures compliance with

regulatory standards, while providing role-based access control to authorized users. In more detail, its functionalities include:

- **Clinical Data Integration and Federation:** The IMS integrates several federated data sources, each of which is a part of the Node Bundles (BNB) distributed in the clinical sites of the BIO-STREAMS project. It provides a unified view of patient information, enabling data analysis and exploration from multiple sites at once. In addition, the IMS offers insights into the connected federated data sources, providing details such as the number of records, types of records, schemas, and other relevant metadata attributes. This information allows users to gain a deeper understanding of the data available in each source and make informed decisions about data utilization and analysis. The metadata functionality enhances data discovery, governance and interoperability, empowering users to navigate and explore the wealth of information across the federated data sources effectively.
- **Data Transaction Tracking:** The IMS maintains a comprehensive audit trail of all data transactions, including data access, retrieval, modification, and deletion. It records user activities, timestamps, and transaction details to ensure accountability, traceability, and compliance with regulatory standards.
- **Access Control and Role-based Authorization:** The IMS is integrated with the authentication and authorization server of the project to verify the identity of users before granting access. Role-based authorization ensures that users only have access to the data and functionalities relevant to their roles and responsibilities. A dedicated board defines roles such as clinicians, researchers, administrators, and patients, each with specific access privileges to different types of data and functionalities within the system.
- **Compliance and Governance:** The IMS considers compliance with regulatory requirements, such as HIPAA (Health Insurance Portability and Accountability Act) and GDPR (General Data Protection Regulation), by implementing encryption on data transfer, and access control measures.

6.4.3 BIO-STREAMS Dashboard

The Dashboard will be the sole entry point to the BIO-STREAMS ecosystem for all stakeholders, enabling them to access all components, offering user-friendly interfaces on individual accounts.

Administrator access will be given to the BIO-STREAMS Board, a committee of BIO-STREAMS Members (acting as a board of directors with a round table structure), that will decide if and/or how new entries will be incorporated in BIO-STREAMS.

List of functionalities:

- Central management of all user accounts and roles.
- Front end for the **BIO-STREAMS Information Management System**, to allow accessing and searching medical data. Viewing of data access audit logs.

- Front end to the **Open Toolkit**, so health professionals and monitors can use the risk assessment tools and the recommendation engine.
- Provisioning of new **BIO-STREAMS Node Bundles** and handling relevant cryptographic material.
- Control of the SSH Server connecting the **BIO-STREAMS Node Bundles**.
- Overview of running status of any other internal cloud services, like **ML Tools**.
- Backend for the ActiveHealth Application (more about this functionality in the next chapter).

6.4.4 BIO-STREAMS ActiveHealth App

The ActiveHealth app and the use of Micro-moments are a main pillar of BIO-STREAMS. In the course of the project, it will be used in two clinical studies:

- Study 2: “Evaluating the impact of a personalized recommendation system for obesity prevention through citizen empowerment and engagement”.
- Study 3: “Preventing obesity through evidence-based recommendations and community-based, family-centric interventions: A Randomized Clinical Trial”.

The application will consist of two parts: The first part will be the “back-office”, a web-based service integrated in the Dashboard that will be used by health professionals monitoring their patients, the end-users of the mobile application. The main functionalities will include:

- Access to Open Toolkit services, like the personalized Risk Assessment Tool and Recommendation Engine (also part of the Dashboard).
- Monitoring patients' intervention progress.

The second part will be the actual mobile application that will be used by parents with children. Its design principles will aim to increase efficiency, personalization, and accessibility, rendering it a holistic tool for fostering healthy habits and catering to individualized family requirements. The main functionalities will be to:

- Deliver personalized lifestyle recommendations tailored to specific goals, with the flexibility to adjust objectives related to activities and nutrition.
- Integrate with the caregivers' therapy protocols by handling personalized data input.
- Monitor personalized progress.
- Provide assistive guidance by allowing access to the Knowledge hub.
- Allow parents to search for specialists in their local area (via the BIO-STREAMS Community Network/Associative Catalogue).
- Seek to motivate users to acknowledge the importance of contributing data using BIO-STREAMS services.

Users will utilize the mobile application to view self-management recommendations related to diet and nutrition and physical activity, and will also fill in a daily diary assessment, documenting e.g.,

what recommendations they follow, patterns and food intake, and psychological markers and activity.

6.4.5 BIO-STREAMS Serious Games Suite

The serious games suite is a service within the BIO-STREAMS Marketplace that supports personalized lifestyle interventions on healthy living (healthy eating and physical activity) and obesity prevention. Its main purpose is to provide gamified exercises on physical activity to increase the level of Intrinsic Capacity (IC) and motivate users to adopt lifestyle recommendations. Competitive avatars will act as life coaches during the physical activity intervention, with users being able to modify programs in a self-paced manner, adjusting goals and strengthening motivation.

The serious games suite aims to integrate both experiential and vicarious learning. In experiential learning, learners engage in direct experiences to enhance their knowledge, skills, and values through human–environment interaction in a cycle of doing, reflecting, concluding, and trying the learned experience. In vicarious learning, individuals learn from the experiences of others. In this manner, individuals can identify difficulties and expectations associated with behaviors and acquire the information and competencies to perform the behavior successfully.

Additionally, behavioral change techniques will be integrated into the serious games suite to generate an attractive and stimulating environment in which knowledge and healthy lifestyle behaviors are encouraged and reinforced. Such techniques include instructions on the ways that a user can perform the behavior, by providing information about health consequences, behavioral practice, behavioral substitution, incentives and rewards, goal setting, reviewing behavior goals, monitoring behaviors, providing feedback on behavior, discrepancies between current behaviors and goals, and monitoring emotion consequences, and prompts or cues.

6.4.6 BIO-STREAMS Risk Assessment and Recommendation Engine

The BIO-STREAMS Open Toolkit will be an AI-driven analytical tool composed of two separate core components: the Risk Assessment Tool and the Recommendation Engine. The main scope of the open toolkit is summarized in the following two (2) points:

- The development of an ML-based model (risk assessment) for the personalized prediction of the risk level of adverse metabolic outcomes attributed to obesity and overweight.
- The development of a rule-based model (recommendation engine) for the delivery of personalized programs of validated lifestyle recommendations for prevention and healthy living.

The risk assessment will make use of retrospective data from multiple sources of the project that will be harmonized and then utilized in the training and development of the risk model. In addition, it will be connected to the knowledge graph, to capture relationships and dependencies between different classes, indicators, and non-obese states. The risk assessment model will be trained by the harmonized retrospective data that reside in the BNBS and contain relevant variables of

anthropometrics, demographics, biospecimens, behavioral data (nutrition, activity), family data, electronic health record and socioeconomics to give predictions of the risk of obesity by defining representative classes for risk assessment. This algorithm will provide age-specific risk stratification, potentially extending to unhealthy metabolic obesity phenotypes.

The recommendation engine's knowledge base will be created and updated based on the content of the public facing website "BIO-STREAMS Knowledge Hub", which is a repository that will contain diverse data sources such as indicators and prognostic biomarkers, published research, and guidelines and interventions. To develop the tool, we will extract relevant features from up-to-date guidelines and research findings, including recommendations, characteristics of children and others, which will then be fed to the recommendation engine and utilized to generate personalized lifestyle recommendations based on validated or widely accepted professional knowledge.

6.4.7 BIO-STREAMS Micro-moments

Micro-moments: Concept and Importance

Micro-moments refer to the brief, spontaneous instances when individuals turn to their mobile devices to act on a need to learn, discover, watch, or buy something. These moments are driven by the intent to act immediately and often are touchpoints where decisions are made, and preferences are shaped. In the context of health behavior, micro-moments can be leveraged to influence healthier choices and improve adherence to health recommendations.

Micro-moments in BIO-STREAMS

In the BIO-STREAMS project, using the ActiveHealth application, micro-moments will take the form of push notifications with recommendations based on the user's profile. These notifications will be tailored to specific instances throughout the day when users are most likely to need guidance or motivation to make healthier choices. The recommendations will be designed to be immediate and relevant, aiming to influence the user's behavior in real-time. In BIO-STREAMS we will address the following main types of micro-moments (the final list of digital interventions implementing micro-moments will be defined through co-creation):

I-want-to-know moments (examples):

- Health Information: Provide access to health information and educational content about healthy eating, exercise, and lifestyle choices. This can be done through search engines or dedicated apps.
- Personalized Advice: Offer personalized advice and recommendations based on user input, such as dietary needs or fitness goals.

I-want-to-go moments (examples):



- Location-Based Services: Develop location-based services that help users find healthy food options, gyms, or parks near their current location.
- Route Planning: Integrate route planning features to encourage users to take walks or bike rides to nearby parks or fitness centers.

I-want-to-do moments (examples):

- Exercise and Fitness: Provide access to exercise routines, workout plans, and fitness tracking tools to help users stay active.
- Meal Planning: Offer meal planning tools and recipes that cater to healthy eating habits.

I-want-to-buy moments (examples):

- Healthy Food Shopping: Develop a shopping list feature that suggests healthy food options and allows users to compare prices and find deals.
- Fitness Equipment: Provide information and reviews on fitness equipment, encouraging users to make informed purchases.

The app will offer immediate, actionable recommendations that align with the user's current context. For example, if a child frequently opts for unhealthy snacks during a specific time of the day, the app might send a reminder about healthier snack alternatives or suggest engaging in a quick physical activity. This approach will ensure that the interventions are timely and relevant, thereby increasing the likelihood of adherence. We will develop engaging and relevant content that meets the needs of users in their micro-moments.

Benefits and Outcomes

The integration of micro-moments in the BIO-STREAMS platform aims to maximize engagement and adherence to healthy lifestyle recommendations. By addressing the impulsive decisions that often lead to unhealthy behaviors, the system provides a practical solution for maintaining long-term health and well-being. The continuous feedback loop ensures that the interventions remain relevant and effective, thereby enhancing the overall impact of the obesity prevention program. By applying the concept of micro-moments to a digital solution for obesity prevention, users will be guided through their daily lives with relevant and timely information, making it easier for them to adopt healthy habits and maintain a healthy lifestyle.

6.5 Data Flow, Data Operations and Data Procedures



6.5.1 Data Oversight

This study involves the collection and processing of personal data, including sensitive data related to children, necessitating rigorous data oversight. To ensure compliance with ethical and legal obligations including the General Data Protection Regulation (GDPR), and to safeguard patient privacy, the study follows closely the legal and ethical practices (with specific focus on the data protection principles) and implements appropriate and state-of-the-art organizational and technical measures.

All data processing will occur in the European Economic Area (EEA) and Switzerland. Each clinical site, contributing with participants, will allocate a pilot leader (e.g. the Principal Investigators) who will oversee the local study and the operations within the pilot study. Project's Clinical Manager, Izidor Mlakar (University of Maribor) will oversee the execution of all the studies. Oversight of the Data Operations will be carried out by Magdalena Góralczyk, Peter Davis and Lucrezia Nicosia (White Label Consultancy APS) and the Project's Data Protection Officer, Dimitris Kalogeras (ICCS). Each clinical partner also has their own DPO (contact details of each provided below).

6.5.2 Categories of Personal Data

6.5.2.1 Co-creation Workshops

The aim of the workshop is not to gather granular information about the workshop participants, but rather, high-level feedback about the proposed intervention study. Nevertheless, the following types of personal data are planned to be processed:

- Basic demographic information, such as age, gender, and school grade
- Responses provided by participants during the co-creation workshops, which may include opinions, perceptions, and experiences shared in response to specific questions

6.5.2.2 Intervention Study

The study will collect the following categories of personal data:

- Secondary data from participants' personal medical records
- Primary data collected through participants' use of BIO-STREAMS mobile application (e.g. behavior, quality of life, activity using the ActiveHealth App and Serious Game suite; see section 2.8.2 for specific questionnaires)
- Primary data collected during the recruitment and baseline clinical data
- Primary data collected through the use of mobile devices
- Genetic data derived from saliva samples

6.5.3 Legal Basis

The processing of personal data for the BIO-STREAMS study (both for the co-creation workshops and for the intervention study) will rely on explicit and informed consent provided by participants and/or their legal guardians, in accordance with the minimum age of consent defined by the national laws applicable at each clinical site.

Participants (and/or their legal guardians) will have the right to withdraw consent for data processing at any stage of the study - before, during, or after data collection - without any consequences or impact on their participation in other educational activities. Upon withdrawal, all associated personal data, whether in physical or digital form, will be securely deleted. Any previously anonymised or aggregated data that cannot be linked to individual participants, hence falling outside the scope of the GDPR, will be retained for research purposes.

Prior to enrolment, all participants will be asked to sign an informed consent form (see Appendices 6 and 7). The accompanying information letter has been developed under a transparent framework informing children and their parents/guardians about the study, its objectives, potential risks and benefits, privacy measures, and the voluntary nature of participation.

The consent materials will be tailored to be age-appropriate, accessible, and engaging, using clear and child-friendly language. They will also be made available in local languages to ensure full comprehension by participants and their families.

This approach is designed to empower children and guardians with the necessary understanding to make an informed decision about participation, and to promote ongoing, open communication between participants and the research team.

6.5.4 Data Collection

Documents collected for the purpose of this clinical investigation will be kept by the organization responsible for clinical investigation until the BIO-STREAMS project is finished. Data collected during the study will be included in their personal medical records and stored at the Investigator's Office in the same way as other personal medical data and information.

Each Principal Investigator at each clinical site is required to maintain records of each subject's case history. Source documents include the participant's hospital files (electronic or paper). The Principal investigator (or members of her/his team) will record which subject is enrolled in this clinical investigation. Access to the subject records and other source data must be provided to study monitors, auditors, and/or inspectors.

6.5.5 Data Sharing and Responsibility of Processing

6.5.5.1 Within the Consortium

Clinical partners (listed below at section 5) are the entities responsible for determining the means and purposes of processing data throughout BIO-STREAMS. Therefore, clinical partners are the designated **controllers** that have chief responsibility for, and control over, observance of data protection principles and respect for data subject rights.

Clinical partners may also, in certain instances in BIO-STREAMS, act as **joint controllers** where the means and purposes of processing are jointly determined by clinical partners. In these cases, Joint Controllorship Agreements (JCAs) will define the responsibilities of each partner to ensure compliance with data protection obligations under GDPR, including handling of access requests, withdrawal of consent, and breach notifications. The clinical partner responsible for collecting the data shall serve as the primary contact point for data subjects. The essence of these arrangements will be made available to data subjects via the informed consent documents and privacy notices. The JCAs will be designed to ensure full transparency, clarity of obligations, and secure collaborative processing across the BIO-STREAMS clinical network.

Technical partners (listed below at section 6) will act as **processors** and can only process personal data under the authority of, and on behalf of, clinical partners acting as controllers. They are responsible for implementing technical and organisational safeguards to ensure data security and privacy but do not independently determine the purpose of processing. If necessary, technical partners may engage sub-processors to assist with data processing activities, but only with the explicit written authorisation of the relevant data controller(s). Where necessary, technical partners may engage sub-processors, but only with the prior written authorisation of the relevant controller(s). To establish clear roles and responsibilities, Data Processing Agreements (DPAs) will be concluded between controllers and processors.

Only pseudonymized personal data, rather than directly identifiable data, will be available to BIO-STREAMS partners. The identifiers available to the BIO-STREAMS consortium are biological sex, age (but not birth date), country/region, and year of first diagnosis.

Only clinical partners (i.e. investigators) will retain the ability to directly identify data subjects from the pseudonymous datasets, for the purpose of a) ensuring data subject rights can be respected (e.g. opt-out, access rights), b) tracking and progress monitoring, and c) ensuring scientific integrity of the data processed.

The investigators will transfer the structured and pseudonymized data required for the study by applying pseudonymization tools to the data contributed by members of the BIO-STREAMS consortium who will use them.

Appropriate pseudonymization techniques and pseudonymization policies (i.e., deterministic pseudonymization, document-randomized pseudonymization, fully randomized pseudonymization) will be selected considering the data protection level, the utility of the pseudonymized dataset and the complexity associated to a certain scheme in terms of implementation and scalability (ENISA, Data Pseudonymization: Advanced Techniques and Use

Cases) (ENISA, Deploying Pseudonymization Techniques). Both basic pseudonymization solutions (e.g., cryptographic hash function, message authentication code, symmetric encryption) and most advanced ones (e.g., Merkle trees, secure multiparty computation, secret sharing schemes) will be investigated according to data pseudonymization requirements.

6.5.5.2 Outside the Consortium

Only anonymized data (including synthetic data) will be shared with 3rd party researchers outside consortium under the Federated Data Storage paradigm (i.e. the BIO-STREAMS Node Bundle), hosted by the BIO-STREAMS Information Management System, with access to be managed by a panel of experts.

6.5.6 Data Subjects' Rights

Clinical and technical partners will implement appropriate organizational and technical measures to ensure that data subject rights are respected. The operationalization of rights to information and access (transparency), rectification (ensuring accuracy), erasure (right to be forgotten), objection, and explanation will be outlined in the Data Management Plan.

6.5.7 Data Storage

6.5.7.1 Database

MongoDB is used for data storage, offering a NoSQL database environment and supporting the dynamic storage needs of the BNB. All necessary configurations for connecting to and interacting with the MongoDB database, ensuring data is securely stored and efficiently accessed will be included.

6.5.7.2 Query Handler

The Query Handler is an advanced component that acts as an intermediary between the backend logic and the MongoDB database, optimizing query execution and data retrieval processes. This custom service enhances the back-end's ability to handle complex data requests, improving response times and overall system performance.

6.5.8 Data Harmonization & Data Curation

Data harmonization aims to address issues related to multiple data sources with varying standards, formats, schemas, structures, and ambiguous semantics, and generate a coherent dataset. The data harmonization pipeline, combining lexical and semantic analysis, will draw upon the BIO-STREAMS common data model and data ontology both aligned with relevant coding

standards and widely adopted protocols to facilitate data interoperability and reusability (Mark et al. 2016) (Wei et al. 2023). In particular, the BIO-STREAMS dataset (data) and dataset descriptor (metadata) will be built in a standardized format by employing a common data model, e.g. the CDISC (“CDISC Standards”) or OMOP (“OMOP Common Data Model”) standards, which comply per se with community standard domain models, terminologies and formats (e.g., ICD10, SNOMED, LOINC). Additionally, the dataset will be contextualized by being associated with the BIO-STREAMS data ontology, providing domain knowledge, which will enhance semantic interoperability. The BIO-STREAMS common data model, ontology and hosting environment, all together, contribute to assuring a high FAIR dataset maturity level (Welter et al., 2023) (“FAIRplus Dataset Maturity (DSM) Model”) (“Changing culture with the Dataset Maturity Model”).

Rigorous data curation and harmonization pipelines will be employed to assure data quality and standardized data representation, respectively^{57,58}. The outcome will be a curated and harmonized dataset, which will be used for the risk factor analysis (i.e., predictive modeling). **Data curation** includes: (i) the assessment of data representativeness through a detailed description of the collected data (e.g., the time span of data collection, the collection site and setting, relevant population characteristics such as gender, age, ethnicity, and relevant medical history, and any inclusion or exclusion criteria that were used), aiming at combating selection bias, and, subsequently, algorithmic bias; and (ii) the assessment of data quality through the detection and description of missing data, outliers (e.g., z-score, isolation forest, elliptic envelope, local outlier factor) and duplicates (based on correlation and lexical matching), considering, in parallel, potential errors in measurement and their underlying mechanisms (e.g., random or systematic), and any known data quality risks and limitations.^{44,45}

Data harmonization will be employed to address issues related to multiple data sources with varying standards, formats, schemas, structures and ambiguous semantics, and generate a coherent dataset. Data harmonization pipelines, combining lexical and semantic analysis, will draw upon the BIO-STREAMS common data model and data ontology, both aligned with relevant coding standards and widely adopted protocols^{59,60} to facilitate data interoperability and reusability^{61,62}.

Data pre-processing, an intermediate layer between data curation/harmonization and predictive modeling, will be employed to handle the identified data quality issues and prepare data for the subsequent phase of predictive modeling. Paradigms of pre-processing steps include removing outliers, deduplication, imputing missing data, transforming variables or creating new features. **Predictive modeling:** Given the BIO-STREAMS feature space, its predictive (prognostic) value with respect to obesity and health outcomes (including comorbidities) will be examined. Machine learning/deep learning algorithms along with statistical analysis will be employed to examine the

⁵⁷ de Hond, A.A.H., et al., npj Digit. Med. 5 (2), 2022. <https://doi.org/10.1038/s41746-021-00549-7>

⁵⁸ World Health Organization. (2023). <https://iris.who.int/handle/10665/373421>. License: CC BY-NC-SA 3.0 IGO.

⁵⁹ <https://www.cdisc.org/standards>

⁶⁰ <https://www.ohdsi.org/data-standardization>

⁶¹ Wilkinson, M., et al. Sci Data 3, 160018 (2016). <https://doi.org/10.1038/sdata.2016.18>

⁶² Rocca-Serra, P., et al. Sci Data 10, 292 (2023). <https://doi.org/10.1038/s41597-023-02166-3>



importance of each feature and identify the most important (i.e., highly ranked) risk factors that affect obesity and health outcomes. Explainable AI methods along with visualization plots will be developed to increase the transparency and interpretability of machine learning and deep learning models.

Standardized data quality evaluation reports will be generated which will be accompanied by data representativeness metadata, with the latter enabling the assessment of selection bias.

6.5.9 Data Retention

Personal data collected for the purposes of this clinical investigation will be retained only for as long as necessary to fulfil the objectives for which it was originally collected. The necessity of continued retention will be periodically reviewed by a panel of experts appointed under the BIO-STREAMS Information Management System. This review will take place at least once every five (5) years following the conclusion of the BIO-STREAMS project.

In accordance with the storage limitation principle, personal data will be securely deleted or anonymized when it is no longer required for the study's purposes. If a data subject (or their legal guardian) withdraws consent or exercises their right to erasure, the data will be deleted or anonymized in accordance with applicable data protection laws.

For the specific purpose of establishing the BIO-STREAMS virtual biobank, only anonymized data will be used, ensuring that no link can be made to any individual. Furthermore, the anonymized data will not be directly stored in the biobank; instead, it will be used to generate synthetic data, which will be stored in the biobank. This approach further limits the impact on individual privacy while enabling continued research and innovation.

6.5.10 Security Measures

BIO-STREAMS project will follow a 'data protection by design and by default' approach. In accordance with the GDPR, appropriate safeguards will be adopted to protect personal data throughout the lifecycle of the study. These measures will be presented during the ethical approval process at each participating institution.

Key security and privacy measures will include:

- The Security Assurance Framework (SAF) ensuring secure and privacy-preserving operation of all BIO-STREAMS components and services, dynamically operating both synchronously and asynchronously. Services include data audit, pseudonymization, anonymization and harmonization, along with the ML-assisted Synthetic Data Generator (SDG) used for anonymized data provision and algorithm training/testing
- The BIO-STREAMS Node Bundle (BNB) including the necessary computer resources for deployment and interconnection within the BIO-STREAMS Hub Network. This network ensures that the BIO-STREAMS Biobank is based on a decentralized federated data management system. The BNB will be installed at every BIO-STREAMS member site to

create a Data Hub, where pseudonymized and standardized datasets are stored locally. All Hubs formulate the Hub Network constituting the BIO-STREAMS Biobank. Data processing tools for harmonization, curation and pseudonymization will be integrated in the backend of BNBs. The connection with the Information Management System (IMS) will be established through associated Application Programming Interfaces (APIs). Security is guaranteed using industry-standard ssh public/private keys. No third-party authorities will be involved.

- To ensure the security and privacy of our systems, we will implement SPHYNX's Security and Privacy Suite. This suite is a comprehensive monitoring service that continuously oversees and evaluates the security posture of an organization's assets in real-time. It's designed to address the foundational principles of Confidentiality, Integrity, and Availability through customizable metrics and an evidence-based methodology, ensuring a certifiable assurance of the system's defenses.
- For authentication and authorization within our system, we will leverage a dedicated security component, which integrates Keycloak for robust identity and access management, alongside KrakenD, an efficient API Gateway, to ensure secure and streamlined access to our resources and services. This security component is designed to enhance the security architecture of applications by providing comprehensive Identity and Access Management (IAM) capabilities, alongside a robust mechanism for exposing RESTful APIs securely. It integrates two essential open-source technologies: Keycloak for IAM, and KrakenD as the API Gateway, working in tandem to ensure secure authentication and authorization processes.

6.6 Study Quality Control Procedures

6.6.1 Study Deviation and Changes

A study deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the Clinical Study Protocol. The investigator is not allowed to deviate from the above-mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless of the reason for the deviation. All major deviations shall be promptly reported to the clinical trial registry. When necessary, ethics reevaluation and an amendment to the ethics approval will be requested.

6.6.2 Methodological Guidelines and Standards

The study will be conducted in accordance with the following guidelines:

- Local country-specific recommendations, regulations, and guidelines,
- GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996) and Guideline for good clinical practice - ICH E6(R2) - EMA/CHMP/ICH/135/1995 (2016),

- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects,
- Clinical Trials Regulation (CTR) EU No 536/2014, (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf),
- The principles defined in the guidelines of Health Technology Assessment agencies / EUnetHTA, in particular, the following will be considered:
 - Comparators & Comparisons. Criteria for the choice of the most appropriate comparator(s). Summary of current policies and best practice recommendations,
 - Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints,
- Medical Device Regulation (MDR 2017/745 EU) (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745>), and
- European legal framework for AI (<https://digital-strategy.ec.europa.eu/en/policies/regulatory-framework-ai>).

6.6.3 Data Review and Processing

During the study, the completeness of patient records will be checked based on the accuracy of entries, the adherence to the protocol and to Good Clinical Practice as well as GDPR protocols, and the progress of enrolment.

Data management will be carried out according to BIO-STREAMS internal procedures as outlined in the Report on Data Management Policy and the Data Management Plan for this clinical investigation. These documents provide further details as to how BIO-STREAMS partners must process data lawfully and ethically and can be made available upon request.

All collected data will be reviewed for completeness, correctness, and consistency, in accordance with the Data Management Plan. In case of issues, queries will be sent to the investigator to complete, correct or comment on the data.

6.6.4 Study Suspension or Early Termination

The study may be terminated or suspended at the initiative of the investigators if any of the following reasons arise:

Data Privacy Concerns: If there are concerns regarding patient privacy and data protection, it may lead to the suspension or termination of the protocol. This could occur if there are breaches in data security, unauthorized access to patient records, or non-compliance with data protection regulations.

Legal or Regulatory Issues: If there are legal or regulatory violations related to the study, such as non-compliance with institutional policies, local regulations, or applicable laws, the protocol procedures may be suspended or terminated to address these issues.

External Factors: External circumstances such as natural disasters, public health emergencies, or unforeseen events that disrupt the healthcare system or impede data access and retrieval from EHRs may necessitate the suspension or termination of the protocol procedures.

In this case, the investigator(s) must inform the Organization responsible for clinical investigation of the reasons for the termination of the study, and the data collected prior to the termination of the study must be passed on to the BIO-STREAMS Platform .

Any changes will be agreed in advance with the Bioethical Committee that authorized the clinical investigation.

6.6.5 Study Close-out

The principal investigator of the clinical site and/or its designees will notify the site of the intention to close the study. Study close-out visits may be performed. During these visits, the monitors will ensure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. The principal investigator of the clinical site and/or its designees will notify and inform the site(s) that all requirements have been met with a study closure letter.

The principal investigator of the clinical site and/or its designees will notify the relevant Bioethical Committee about the clinical trials closure by providing a Clinical Studies report based on the Bioethical Committee/another regulatory authority form.

The Clinical Coordinator of the BIO-STREAMS Studies will update the information in the relevant study registry accordingly.

6.6.6 Data Reporting and Publication

Any deviations from the CIP will be described and justified in the Final Clinical Study Report, as appropriate.

Publications and presentations referring to this clinical study will be coordinated by the Principal Investigators of the Clinical Sites, Izidor Mlakar (acting as the clinical coordinator of BIO-STREAMS Studies) and the Project's Data Protection Officer, Dimitris Kalogeras (ICCS) to ensure privacy preserving use of all available data and confidentiality of shared results.

The study will be registered, and progress and results of the study will be regularly updated at the public clinical study registry, ISRCTN Registry (<https://www.isrctn.com>).

6.6.7 Adverse Effects Monitoring and Reporting

In this study, no adverse effects are expected. During the recruitment phase the risk for severe adverse events will be re-evaluated for each perspective participant. During the execution of the study the study personnel will monitor participants for adverse effects throughout the duration of their involvement in the study using the following methods of monitoring:

- Regular check-ins: Participants will be asked to report any adverse effects during follow-up visits, interviews, or interactions with study personnel.
- Passive monitoring: Monitoring of digital intervention usage data for signs of adverse effects, such as increased stress levels or discontinuation of use.
- Adverse event logs: Study personnel will maintain detailed logs of any adverse events reported by participants or observed during the study.

6.6.7.1 Response and Management

Adverse effects monitoring and reporting procedures will prioritize participant safety and well-being, ensuring that their rights and dignity are respected at all times. Adverse effects will be reported promptly to the pilot site's principal investigator, the clinical coordinator of the BIO-STREAMS project and relevant Institutional Review Boards (IRBs) or ethics committees. Adverse effects reporting will be conducted in accordance with ethical principles of autonomy, beneficence, and non-maleficence, with a focus on minimizing harm to participants.

The overall response to adverse effects includes the following:

- Immediate action: Study personnel will take immediate steps to address any adverse effects reported by participants, including providing medical assistance if necessary.
- Follow-up: Participants experiencing adverse effects will be monitored closely, and appropriate follow-up care will be provided as needed.
- Transparent communication: Participants will be informed of any adverse effects they experience and provided with information on how they will be managed.
- Support and reassurance: Participants will be offered support and reassurance throughout the process, including access to counselling or psychological support if needed.

The minimal reporting requirements will include:

- Severity assessment: Adverse effects will be assessed for severity using standardized criteria (e.g., mild, moderate, severe) to determine appropriate reporting procedures.
- Documentation: Detailed documentation of each adverse event, including its nature, severity, duration, and resolution, will be maintained in the study records.
- Reporting to regulatory authorities: Serious adverse events (SAEs) will be reported to regulatory authorities as per regulatory requirements and institutional policies.

The standardized reporting format to document adverse effects will include:

- Date and time of event
- Description of event



- Severity assessment
- Actions taken in response
- Follow-up plan
- Any additional relevant information

6.7 Pilot Sites

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Title of the department (s): Physiotherapy and rehabilitation for children

DPO: Benislav Vatev; e-mail: b.vatev@bozhikov-vatev.bg.

Principal investigator: Assoc. prof. Radka Savova, MD, PhD (savova.radka@gmail.com)

Research team: Assoc. prof. Radka Savova, MD, PhD (savova.radka@gmail.com), Svetlin Hansov (svetlin.hansov@blocks.care)

Research center No 5: Hospital Universitari Vall d'Hebron

Address: Pg. de la Vall d'Hebron, 129, Horta-Guinardó, 08035 Barcelona, Spain

Tel: +34 934 89 30 00

Title of the department (s): Vall d'Hebron Institut de Recerca

DPO: Fundació Tic Salut Social, email: dpd@ticsalutsocial.cat.

Principal investigator: Andreea Ciudin. Email: andreea.ciudin@vallhebron.cat

Research team: Andreea Ciudin. Email: andreea.ciudin@vallhebron.cat

Research center No 6: Centre Hospitalier Universitaire de Liège

Address: Avenue de l'Hôpital, 1 4000 Liège, Belgium

Tel: +32(0)4.323.00.00; Fax: N/A ; e-mail: info@chuliege.be

Title of the department (s): Department of Pediatrics

Tel:+32(0)4.323.92.00; Fax:N/A ; e-mail: N/A

DPO: Ghislaine Dumont; e-mail : ghislaine.dumont@chuliege.be

Principal investigator: Dr. Caroline Gernay (cgernay@chuliege.be)

Research team: Dr. Caroline Gernay, Dr. Marie-Christine Lebrethon, Zheshen Jiang, Nicolas Gillain.

Research center No 7: Penteli General Children's Hospital

Address: Ippokratous 8 15236

Tel: +302132052507.; e-mail: info@biostreams-penteli.eu.

Title of the department (s):Penteli General Children's Hospital

Tel: +302132052507 e-mail: info@biostreams-penteli.eu.

DPO: Antonia Andriopoulou e-mail: dpo@paidon-pentelis.gr

Principal investigator: Georgios Gkritzelas

Research team: ...Olga Fafoula, Athina Balaska, Athanasia Harokopou, Andriana koulountzou, Georgios Feretzakis, Georgios Zagkavieros, Efstathia katoikou , ilias Dalainas

6.8 Data Processors for the Intervention Study

Research partner No 1: University of Maribor

Address: Koroška cesta 46, 2000 Maribor

Title of the department (s): Laboratory for Digital Signal Processing

Principal investigator: dr. Izidor Mlakar, e-mail: izidor.mlakar@um.si

DPO: doc. dr. Miha Dvojmoč (dpo@um.si)

Research team: dr. Urška Smrke (urska.smrke@um.si)

Reason for data access: clinical coordination and updates to public study registry, coordination and publication of results, public dissemination

Research partner No 2: PANEPISTIMIO IOANNINON (UOI)

Address: PANEPISTEMIOYPOLE PANEPISTEMIO IOANNINON, IOANNINA 45110, Greece

Title of the department (s): Department of Materials Science and Engineering, Unit of Medical Technology and Intelligent Information Systems

Principal investigator: Prof. Dimitrios I. Fotiadis, e-mail: fotiadis@uoi.gr

Research team: Eleni Georga (egeorga@uoi.gr), Marina Georgoula (mgeorgoula@uoi.gr), Orestis Papagiannopoulos (orepap@uoi.gr), Daphne Katsarou (d.katsarou@uoi.gr), Konstantinos Mavrokotas (k.mavrokotas@uoi.gr), Evgenia Lampropoulou (lampropoulouevgenia@gmail.com)

DPO: Stavroula Stathara (dpo@uoi.gr)

Reason for data access: data curation, data harmonization, data pre-processing, machine learning and deep learning predictive modeling, data anonymization / pseudonymization.

Research partner No 3: Computer Solutions Cyprus LTD (CSCY)

Address: Diagorou 4, KERMIA BUILDING, 8th fl. 802, 1097, Nicosia, Cyprus

Title of the department (s): R&D

Principal investigator: Dr Stavros Pitoglou (s.pitoglou@csl.gr)

Research team: Dr Thelma Androutsou (t.androutsou@csl.gr), Ioannis-Andreas Filippas (i.filippas@csl.gr)

DPO: Athanasios Spetsarias (a.spetsarias@csl.gr)

Reason for data access: data API development, data curation, data harmonization, data pre-processing, machine learning and deep learning predictive modeling, data anonymization / pseudonymization.

Research partner No 4: Novelcore (NVCR)

Address: Mavromichali 104, Athina 114 72

Title of the department (s): Novelcore

Principal investigator: Georgios Domalis (domalis@novelcore.eu)

Research team: Ioannis Livieris (livieris@novelcore.eu), Nikolaos Alimpertis (alimpertis@novelcore.eu)

DPO: Dimitrios Charalampakis (charalampakis@novelcore.eu),

Reason for data access: data pre-processing, data enrichment, synthetic data generation, knowledge graph creation, data evaluation.

Research partner No 5: Ainigma technologies (AINIGMA)

Address: Kapeldreef 60 - Leuven 3001, Belgium

Title of the department (s): RnD

Principal investigator: Athanasios Kakasis (kakasisathan@ainigma.tech)

Research team: Christos Chatzichristos (cchatzic@ainigma.tech), Ali Saad (a.saad@ainigma.tech), Marianna Panagiotidou (m.panagiotidou@ainigma.tech)

DPO: Athanasios Kakasis (kakasisathan@ainigma.tech)

Reason for data access: data pre-processing, machine learning and deep learning predictive modeling

Research partner No 6: HAROKOPIO UNIVERSITY OF ATHENS (HUA)

Address: El. Venizelou 70, Kallithea, 176 71 Athens, Greece

Title of the department(s): Department of Informatics and Telematics

Principal investigator: Associate Prof. George Dimitrakopolos, e-mail: gdimitra@hua.gr

Research team: George Dimitrakopoulos (gdimitra@hua.gr), Ilias Panagiotopoulos (ipanagio@hua.gr), Christina-Athanasia Alexandropoulou (calexand@hua.gr), Yioula Lekka (ylekka@hua.gr), Despoina Mitsiogianni (it219146@hua.gr)

Reason for data access: data curation, data harmonization, data pre-processing, machine learning and deep learning predictive modeling, data anonymization / pseudonymization.

Research partner No 7: Innovation to Grow (i2G)

Address: Via A. Appiani 12, 20121 Milano, Italy

Title of the department (s): Innovation Dept.

Principal investigator: Umberto Restelli (u.restelli@i2grow.it)

Research team: Sofia Silvola (s.silvola@i2grow.it)

DPO: Matteo Colombo (m.colombo@i2grow.it)

Reason for data access: assessment of resources used and cost data. Analysis of available data for health economic indicators implementation

Research partner No 8: Telematic Medical Applications Ltd (TMA)

Address: 151 Al. Papanastasiou Ave. 18533, Piraeus, Greece

Title of the department (s): Software Development

Principal investigator: Philipos Sotiriadis, e-mail: philsot@tma.gr

Research team: Harilaos Kakoulidis, Emmanouil Georgoudakis, Marios Prasinos, Marios Kanaris, Marsel Otska

DPO: Angelos Kynigalakis, e-mail: akynigalakis@tma.gr

Reason for data access: Development of the BIO-STREAMS Dashboard and ActiveHealth mobile application.

Research partner No 9: UKEMED GLOBAL Ltd (UKEMED)

Address: 121, Prodromou Street Offices 713-715 2064, Nicosia, Cyprus

Title of the department (s): Innovation and Research

Principal investigator: Iliana Korma (i.korma@gmail.com)

Research team: Zenia Koti (zeniakoti@ukemed.com), Chara Kapsala (chara.kapsala@ukemedglobal.com)

DPO: Takis Kotis (takiskotis@ukemedglobal.com)

Reason for data access: assessment of resources used and cost data. Analysis of available data for health economic indicators implementation, public dissemination.

Research partner No 10: TECREANDO B.V. (TCR)

Address: Herengracht 575-577, 1017 CD, Amsterdam, the Netherlands

Title of the department (s): N/A

Principal investigator: Sotiris Pavlopoulos (pavlopoulos@tecreando.com)

Research team: Ioannis Vezakis (vezakis@tecreando.com)

DPO: Panagiotis Tsatsoulis (tsatsoulis@tecreando.com)

Reason for data access: Data harmonization, data analysis, machine learning and predictive modeling

Research partner No 12: EREVNITIKO PANEPISTIMIAKO INSTITOUTO SYSTIMATON EPIKOINONION KAI YPOLGISTON-EMP (ICCS)

Address: PATISION 42, ATHINA 106 82, Greece

Title of the department (s): Biomedical Engineering Laboratory (BEL) of the School of Electrical and Computer Engineering (ECE) of the National Technical University of Athens (NTUA)

Principal investigator: Prof. D. Koutsouris (dkoutsou@biomed.ntua.gr)

Research team: E. Vellidou (ebel@biomed.ntua.gr), I. Kakkos (ikakkos@biomed.ntua.gr), I. Kouris (ikouris@biomed.ntua.gr), A. Anastasiou (aanastasiou@biomed.ntua.gr), K. Bromis (konbromis@biomed.ntua.gr), V. Apostolakos (vapostolakos@biomed.ntua.gr)

DPO: Dimitris Kalogeras (dkalog@gmail.com)

Reason for data access: Data collection, data curation, data harmonization, data pre-processing, machine learning and deep learning predictive modeling, data anonymization / pseudonymization.


6.9 Study financing

This study is part of the BIO-STREAMS European Project funded within the research and innovation program of the Horizon Europe under N° 101080718. The funding source had no impact on the decision to carry out the study or in its design. The funding source will have no impact on the decisions related to publishing this research or its outcomes. The content of this document does not reflect the official opinion of the European Union or any other institution.

6.10 Appendices

6.10.1 Co-creation Workshop Materials

Appendix 1: Child Persona Description

	<p>Background info</p> <p>Name: Jane Age: 9 years Role: child with excess weight</p> <p>Jane lives with her sister and parents in a suburban house. She plays tennis on a weekly basis for one hour and enjoys regular sports class twice a week in school. Every day after school, her mom prepares a pre-cooked meal for the family.</p>	<p>What are her needs?</p> <p>Jane's needs are to receive knowledge on a healthy lifestyle and to get engaging information and, most importantly, to receive enough encouragement from her parents, peers, and teachers. Her need is also to reduce sedentary behavior and, when she is older, to take charge of her own weight management.</p> <p>More specifically:</p> <ul style="list-style-type: none"> • <u>Fun and Engaging Learning</u>: Jane needs a platform that turns learning about nutrition and exercise into a fun and interactive experience. For instance, interactive games that teach her about healthy food choices and the importance of physical activity. • <u>Peer and Parent Approval</u>: Jane seeks approval from her friends and family. The platform should have features that allow her to share achievements with peers and receive positive feedback from both friends and parents. • <u>Encouragement and Positive Reinforcement</u>: Jane requires regular encouragement to stay motivated. Personalized messages, virtual rewards, and a system that acknowledges her progress can be crucial in keeping her engaged. • <u>Knowledge of a Healthy Lifestyle</u>: Jane needs easily digestible information about healthy eating habits and the benefits of an active lifestyle. Animated videos or infographics that break down these concepts in a child-friendly manner would be ideal. • <u>Taking Charge of Health</u>: Jane wants to feel in control of her health journey. The platform should provide her with tools, like setting personal goals or creating a virtual avatar, to empower her to make positive choices.
	<p>What are her goals?</p> <p>Children do not fully grasp the idea of goals yet at that age. Her goal is to have fun, interact with peers, and to have peer and parent approval. However, when they become teenagers, they begin forming ambitions for themselves. One ambition related to obesity prevention is to have a healthy relationship with her own body and another is to reduce sedentary behavior.</p>	
	<p>What can Jane benefit from BIO-STREAMS?</p> <p>Jane is looking to have fun with activities she engages in. By using BIO-STREAMS, she will benefit by indirectly changing her lifestyle habits and improving her self-esteem. The solution will offer her guidance on weight management. This guidance will focus on promoting the principles of a healthy lifestyle and not weight loss per se, therefore the stigma around overweight/obesity will be smaller, which will cause lesser pressure on her.</p>	<p>What digital functions does she seek?</p> <p>Jane benefits from different functions in her digital devices. She likes to connect with her peers and engage in interactive activities. She likes to play electronic games or use apps with gamified elements. However, her smartphone and/or tablet use should not be without the parents' surveillance. When Jane becomes a teenager, she will benefit from personalized recommendations in the app and an individualized nutrition plan.</p> <p>More specifically, examples of digital solutions sought are:</p> <ul style="list-style-type: none"> • <u>Interactive Mobile Apps</u>: An app that she can access on her tablet or her smartphone, incorporating gamified elements and interactive features to make it enjoyable for her.
<p>What is her motivation?</p> <p>Jane is motivated by her well-being and happiness, which resonates with mental health in people her age. She is highly motivated by peers' opinion and approval. Sometimes, she is a victim of bullying at her school, which also</p>		

<p>impacts her self-esteem in a negative way. She enjoys physical activity which also helps her with health issues prevention. She does not bother herself with health issues; however, her parents do, and she seeks their approval. Lastly, she is also motivated by competing with her peers.</p>	<ul style="list-style-type: none"> • <u>Virtual Rewards System:</u> A system that rewards her with virtual badges, stars, or other symbols of achievement for completing daily exercises or making healthy food choices. • <u>Family-Friendly Challenges:</u> Challenges that involve the whole family, fostering a supportive environment for Jane and encouraging healthy habits for everyone. • <u>Progress Tracking and Visualization:</u> A feature that allows Jane and her parents to track her progress visually, providing a sense of accomplishment and motivation for continued engagement. • <u>Parent-Child Interaction Tools:</u> Features that facilitate communication between Jane, her parents, and potentially her teachers, fostering a collaborative effort in her weight management journey.
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Figure 7: Child Persona Description

Appendix 2: Questions for Input on Child Persona

Open-ended questions

- Do you think this Persona represents people from your age group?
- Is there something that you think should be modified?
- Do you understand this Persona?
- Do you think the picture matches the Persona description? Is it authentic?
- Can you imagine a day in a life of this Persona?

Appendix 3: Questions for Input on User Requirements, Study Design and Intervention

Version for adolescents

Healthy eating

- B1 What is healthy lifestyle to you?
- B2 Are there specific topics related to health that you are curious about?
- B3 What do you think is important to know about healthy lifestyle?
- B4 Through which channels/devices do you prefer to learn about healthy eating habits and physical activity?

B5 How are healthy habits promoted at home?

Healthy lifestyle literacy

D2 Can you think of any health goals you might want to set for yourself?

Healthy lifestyle (general) and motivation

A1 What kind of activities do you find fun?

A1.3 What do you think makes these activities enjoyable for you?

A2 Can you tell me about a game or activity you enjoy on your devices (phone, tablet, computer)?

Trust in interventions and in guidance (adherence)

E2 What kind of app features do you find most interesting or enjoyable?

Platform presentation if not before

Physical activity and sedentary behavior

C2 What kind of features would you like to see on the platform?

C5 What kind of progress tracking tools would you find helpful?

The platform

F1 What kind of personalized recommendations would be helpful for you in the app? (e.g. healthy recipes, recommended fruit intake, recommended sport activities)

F2 Are there specific aspects of nutrition or physical activity you would like guidance on?

Biosampling

G1 Would you be comfortable with a nurse taking two swabs of your inner cheek to collect saliva?

G1.1 Would you rather do it yourself?

Version for younger children

Healthy eating

- B1 What is healthy lifestyle to you?
- B2 Are there specific topics related to health that you are curious about?
- B4 Where do you like to learn about healthy food and sport activities?

- B5 What healthy things do you do at home?

Healthy lifestyle literacy

- D2 Do you want or wish for anything regarding being healthy?

Healthy lifestyle (general) and motivation

- A1 What kind of activities do you find fun?
- A1.3 What do you think makes these activities enjoyable for you?
- A2 Can you tell me about a game or activity you enjoy on your phone, tablet, computer?

Trust in interventions and in guidance (adherence)

- E2 What do you like on the apps and games that you play?

Platform presentation if not before

The platform

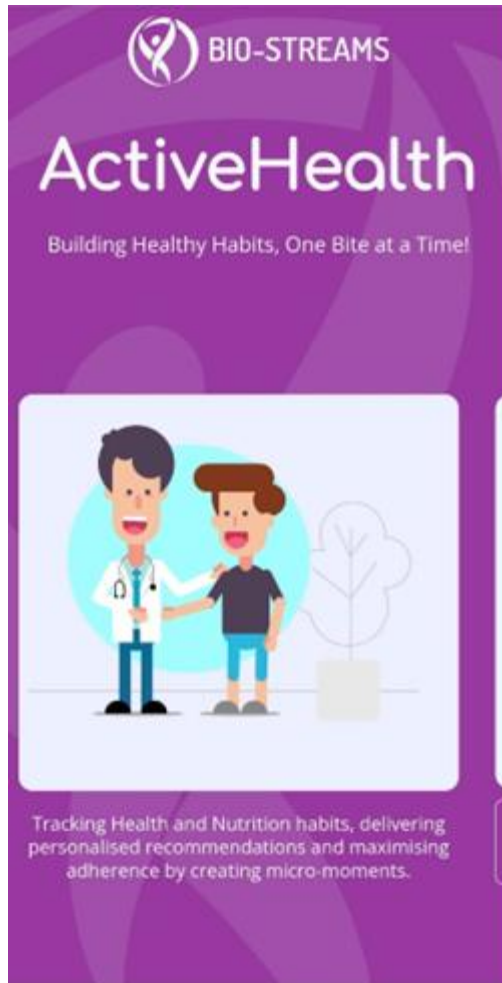
F1 Imagine a 'healthy app'. What would you want this app to teach you or help you with?

Biosampling

G1 Would you be comfortable with a nurse taking two swabs of your inner cheek to collect saliva?

G1.1 Would you rather do it yourself?


Appendix 4: BIO-STREAMS ActiveHealth App Mock-ups



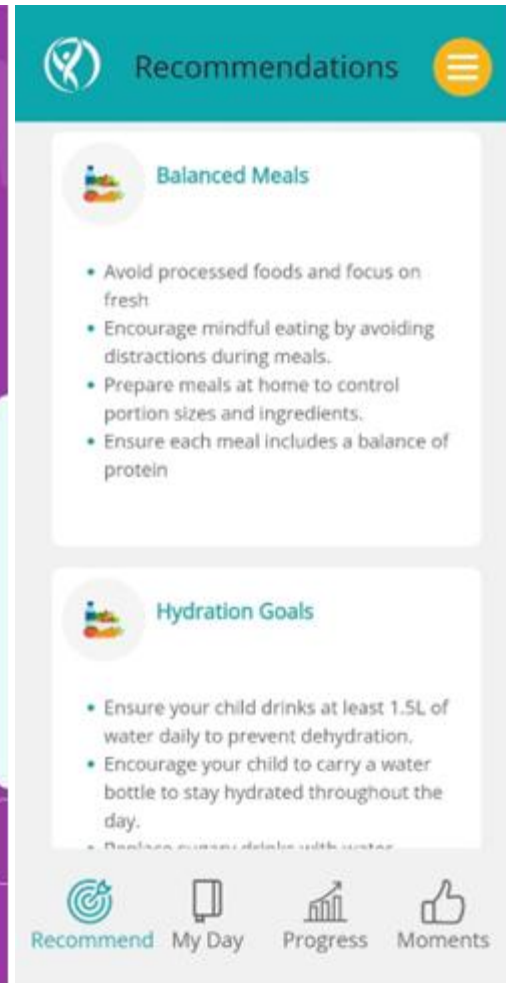
BIO-STREAMS

ActiveHealth

Building Healthy Habits, One Bite at a Time!



Tracking Health and Nutrition habits, delivering personalised recommendations and maximising adherence by creating micro-moments.



Recommendations

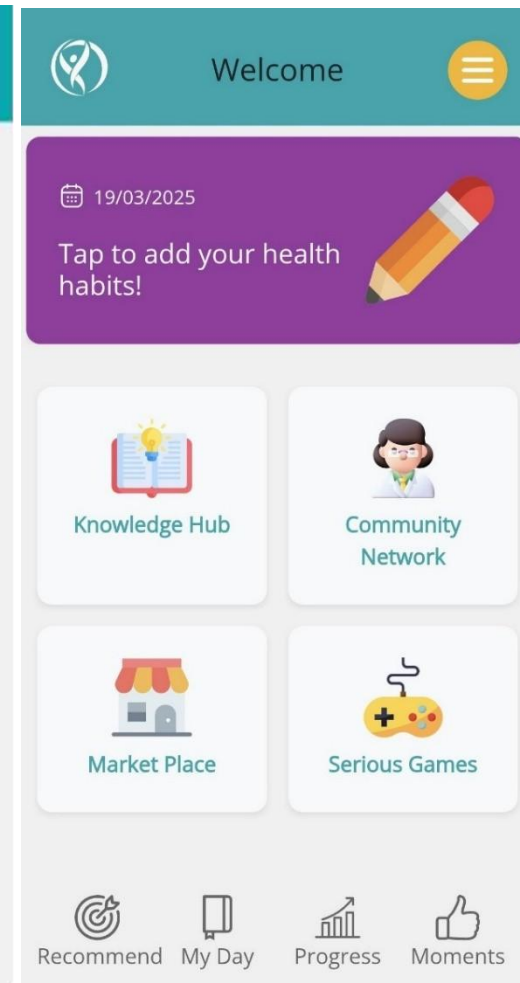
Balanced Meals

- Avoid processed foods and focus on fresh
- Encourage mindful eating by avoiding distractions during meals.
- Prepare meals at home to control portion sizes and ingredients.
- Ensure each meal includes a balance of protein

Hydration Goals

- Ensure your child drinks at least 1.5L of water daily to prevent dehydration.
- Encourage your child to carry a water bottle to stay hydrated throughout the day.
- Replace every drink with water.

Recommend My Day Progress Moments



Welcome

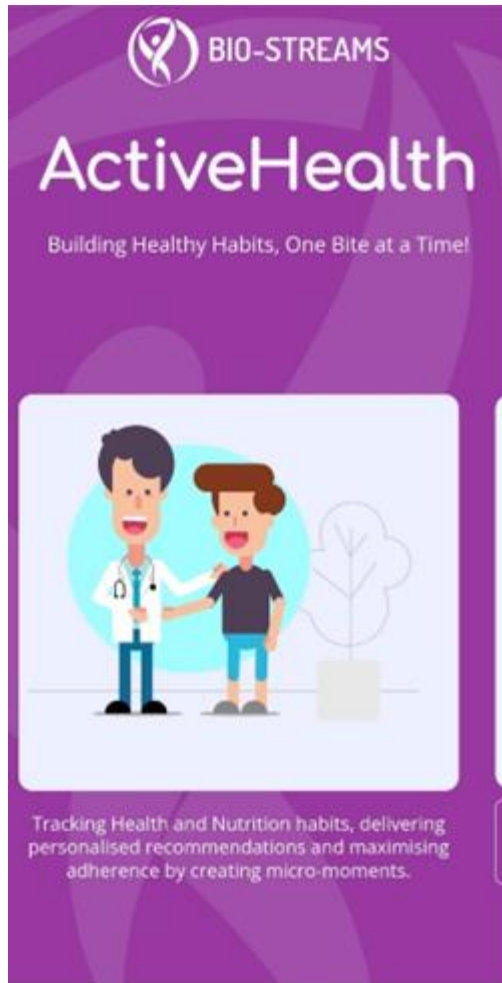
19/03/2025

Tap to add your health habits!

Knowledge Hub Community Network

Market Place Serious Games


Recommend My Day Progress Moments



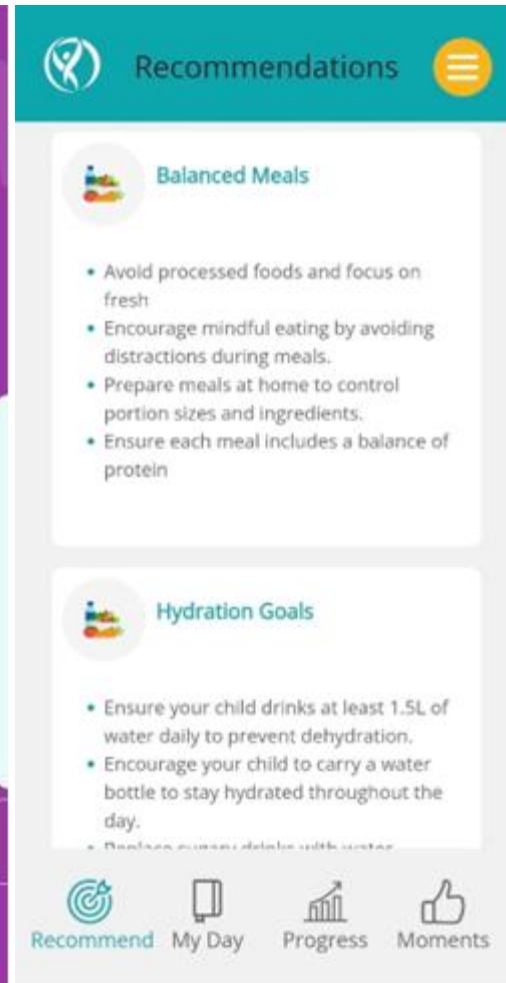
BIO-STREAMS

ActiveHealth

Building Healthy Habits, One Bite at a Time!



Tracking Health and Nutrition habits, delivering personalised recommendations and maximising adherence by creating micro-moments.



Recommendations

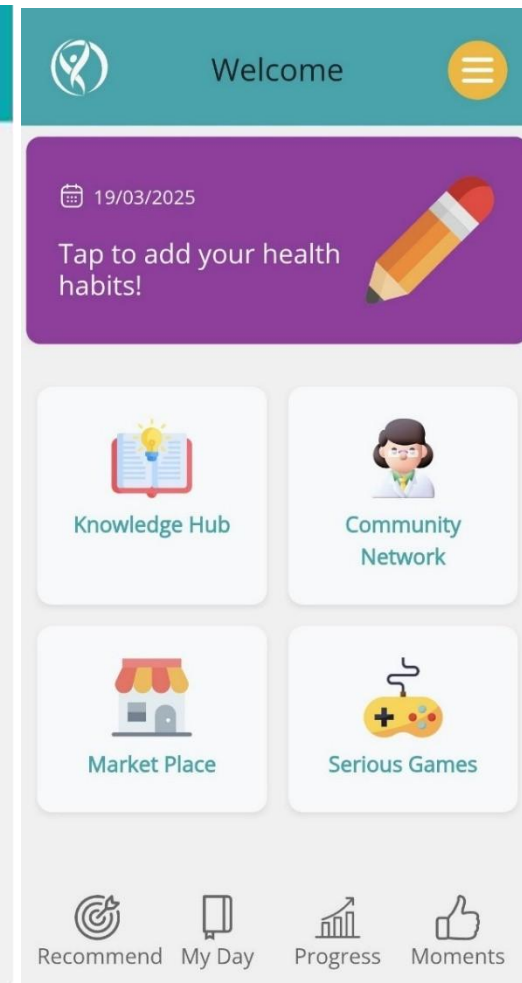
Balanced Meals

- Avoid processed foods and focus on fresh
- Encourage mindful eating by avoiding distractions during meals.
- Prepare meals at home to control portion sizes and ingredients.
- Ensure each meal includes a balance of protein

Hydration Goals

- Ensure your child drinks at least 1.5L of water daily to prevent dehydration.
- Encourage your child to carry a water bottle to stay hydrated throughout the day.
- Replace every drink with water.

Recommend My Day Progress Moments



Welcome

19/03/2025

Tap to add your health habits!

Knowledge Hub Community Network

Market Place Serious Games

Recommend My Day Progress Moments

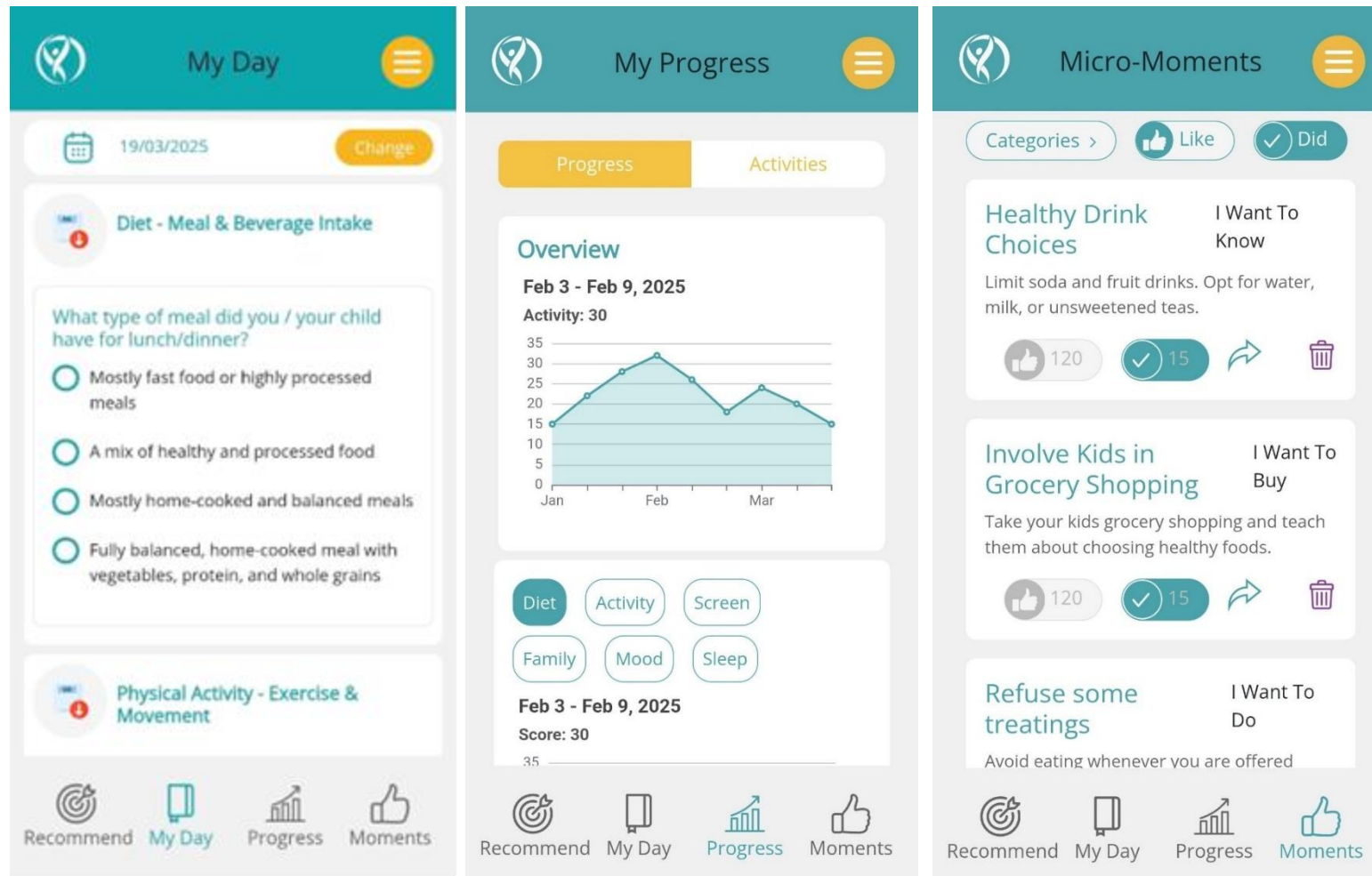


Figure 8: BIO-STREAMS ActiveHealth App mock-ups

Appendix 5: Serious Games mock-ups

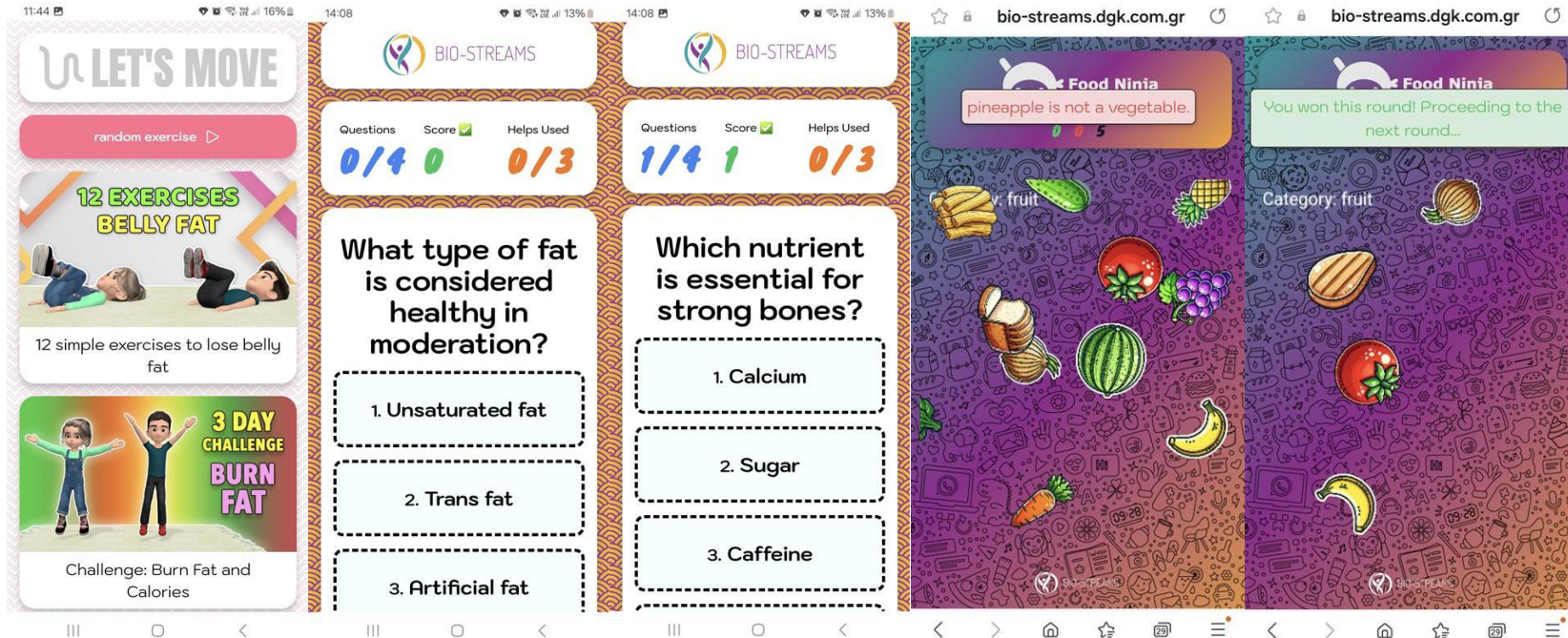


Figure 9: Let's move, Food quiz, and Fruit ninja mock-ups

Appendix 6: Consent form Package for Co-creation Workshops

Information on consent forms and letters for co-creation workshops and the intervention study (Appendix 7) might differ. This is because intervention study is being prepared several months after the co-creation workshops and new information regarding data handling and privacy has been added to the letters and texts adapted accordingly.

BIO-STREAMS Workshop Information Letter to Parents/Guardians and Competent Children

[Date]



Introduction

We are inviting you (or your child) to take part in a **co-creation workshop** relating to the **BIO-STREAMS project**, which aims to help you (or your child), your peers, and your family, to maintain a healthy lifestyle through education and digital tools. BIO-STREAMS also aims to facilitate and conduct scientific research on childhood obesity based on data collected from children with and without obesity across the EU.

A significant part of BIO-STREAMS is to get input from children directly about our plans to research and improve weight-related health. We plan to organize two different co-creation workshop sessions lasting for 90 minutes each to engage, collaborate with, and gather feedback from children between 5 and 18 years old about topics related to health. This way, you (or your child) will shape the direction of our project and – we hope – help to create a positive impact on public health.

As you may be aware, overweight and obesity rates have reached epidemic proportions across the EU, and continue to grow. Innovative solutions are required to prevent, improve, and better understand this epidemic. The BIO-STREAMS project is primarily dedicated towards understanding genetic and environmental causes of obesity and excess weight, and whether digital tools like apps and games can improve children's and adolescents' health. Early-age interventions are known to be a key piece of this puzzle, potentially having long-term beneficial outcomes for health throughout life, which is why we are focusing on children under the age of 18.

The co-creation workshop that you are invited to is aimed at making sure our plans are user-centric, culturally sensitive, ethical, and effective. We will do this by introducing a series of topics, such as an idea for a health-related phone application, and discussing with you (or your child), together with children of similar age, in a collaborative and age-appropriate manner.

Before you decide whether to participate in this study and sign the consent form, or do so for your child, please take your time to read this information letter. If there is something you do not

understand, or if you would like more information, please ask us. It is important that you fully comprehend what participation in this project entails. Please also note that there is a simplified version of this information letter on page 61.

Who are we?

We are researchers from [BEN name] working under the European Union Horizon Europe Program funded BIO-STREAMS project (*Multi-Pillar Framework For Children Anti-Obesity Behaviour Building On An EU Biobank, Micro Moments And Mobile Recommendation Systems, Approval Number 101080718*) together with 29 partners from 15 European countries. Our team is led by [PI name] and you can reach us using this e-mail address: [PI's email].

We are one of seven clinical research partners based across Belgium, Bulgaria, Greece, Spain, Sweden and Slovenia. The BIO-STREAMS project also involves other European organizations with other forms of expertise, such as in technology, education, law, and project management. However, we at [BEN name] will be the main organization that you will interact with, and you should reach out to us if you have any issues or questions.

What does the study involve?

We are recruiting children aged 5-18, both with and without overweight or obesity.

You (or your child's) participation will involve their attendance at, and participation in, two 90-minute workshop sessions. In these, we aim to introduce ourselves, our project, and talk about the need for children's and adolescents' voices to shape health-based initiatives like BIO-STREAMS. After, we will brainstorm ideas and concepts for BIO-STREAMS through discussion, games, role-playing and/or drawings.

From these interactions, we will collect information about the responses using child-friendly methods (we will not take audio or visual recordings of the workshops) and use that to refine our future plans. We will also share these insights with other including educators, healthcare professionals, and policymakers, to ensure that children and adolescents' voices are heard in the design and implementation of obesity prevention interventions.

Benefits of Participation

Whilst the main benefits of the project are the betterment of public health, and the improvement of scientific knowledge, you and/or your child may benefit from improved understanding of health-related behaviors. No compensation, beyond direct costs related to study (e.g. organized visits to the pilot sites) is provided.

Risks and Discomforts of Participation

Your child may experience some emotional distress from discussing sensitive topics. As with any medical research project that involves personal data, there is also a risk of a data breach.

However, we have taken, and will take, steps to minimize these risks, including the provision of psychological support, if necessary, implementation of strict confidentiality measures and protocols, and the right to withdraw from the study at any time.

Privacy and Confidentiality

Our goal is not to collect detailed individual responses from participants, but to gather an overall picture of the responses to discussion in the workshop sessions. Therefore, directly identifying information such as addresses, dates of birth and full names will not be collected as part of the workshop's results.

However, we will still process certain personal data about you and/or your child, including identifying information, in order to ensure you are (or your child is) suitable for the workshop, to gather requisite consent, and to ensure we can contact you if the need arises. We may also further process data that relates to you (or your child), including anonymizing data. Only we will have access to your personal data. We will only share anonymous data with our project's partners and outside of the project.

All personal data will be kept confidential and stored securely in compliance with applicable law, including the General Data Protection Regulation (GDPR). Please see the Privacy Notice attached to this form for further information.

Voluntary Participation

Participation in the co-creation workshop is entirely voluntary, and participants have the right to refuse or withdraw at any time without consequences. Refusal to participate, or withdrawal from participation, will not affect your child's access to healthcare or other services.

Consent

Participation in the study requires giving consent, which means that you allow you (or your child's) personal information for the purposes of the workshop, and for a variety of future publications of its results but which cannot be specified at the present time.

Legal guardians must provide consent on behalf of children and adolescents under X years of age. If the participant is between the ages of Y and X years, we would like them to also sign the consent form, to show that they are willing to participate. If the child is under Y years, we will also ask them to assent to participation in the study, depending on their ability to understand the project.

Contact Details

If you would like more information, you may call us. You are welcome to call us at any time before or during the study, with questions and/or concerns, or if you would like to withdraw yourself (or your child) from the study. You can contact [*insert contact details here*].

Conclusion

We very much appreciate your consideration in participating in BIO-STREAMS co-creation workshops, which we hope will have a meaningful impact on public health and scientific research. If you agree to your child's participation, please read and sign the consent form below.

BIO-STREAMS Simplified Information Letter

[Actual Date]



Hello!

We're inviting you to join a workshop for a project called BIO-STREAMS. This project is all about helping kids like you, your friends, and your family to stay healthy and happy. We're also doing some important research about childhood overweight.

What's the project about?

You might know that there are more and more kids and adults in Europe who have problems with weight. This is a big problem, and we need new ways to help people to maintain a healthy lifestyle. That's where BIO-STREAMS comes in. We're trying to understand how digital tools like apps and games can help kids stay healthy.

What will you do in the workshop?

We're planning two fun workshops that will last for 90 minutes each. In these workshops, we'll talk about health and come up with ideas for the BIO-STREAMS project. You'll get to share your thoughts and ideas and do some fun activities too!

Who are we?

We're a team of researchers from [BEN name], and we're working on this project with lots of other people from 15 different countries in Europe. If you have any questions or if something is bothering you, you or your parent or guardian can always reach out to us.

What will happen in the study?

If you decide to join us, you'll take part in two workshop sessions. We'll talk about health, do some fun activities, and you'll get to share your ideas about how we can help kids stay healthy. We won't record the workshops, but we'll take notes so we can remember all the great ideas you come up with!

What's good about joining?

By joining, you'll learn more about staying healthy. Plus, your ideas could help other kids stay healthy too!

Are there any risks?

Sometimes, talking about sensitive topics can make people feel uncomfortable. But don't worry, we'll do our best to make sure everyone feels safe and respected. If you don't feel comfortable, please let us know. And remember, you can always choose to stop participating at any time.

What about your privacy?

We won't collect any personal information like your full name or address during the workshops. But we will need some information about you to make sure you can participate and to get your permission to join. We promise to do our best keep all your information safe and private.

Do you want to join?

Joining is totally up to you, and it's okay to say no. If you want to join, you and your parents will need to give permission by signing a consent form.

Need more info?

If you have any questions, you can always ask us. You can contact us at [insert contact details here] or ask your parent or guardian to do so for you.

Thank you!

We really appreciate you considering joining our BIO-STREAMS workshops. We hope you'll decide to join us in making a positive impact on health and science!

Declaration of Consent – Parent or Legal Guardian



Participation of a minor in the BIO-STREAMS project study:

Child’s name:

Child’s date of birth:

	YES	NO
I understand what this research is about.		
I understand what my child’s role in the research will be, what they will be doing.		
I know what data will be collected about my child, and how it will be processed.		
I have been able to ask questions and get answers.		
I am happy for my child to participate in this activity and be part of the research.		
I know that I can withdraw my consent at any time and I know who to contact.		
I agree that my child may participate in the BIO-STREAMS project workshop at [BEN] led by [PI’s name]		
I consent to my child’s personal data being processed for the purposes of the BIO-STREAMS project workshop.		

I consent to my child’s personal data to be used for future publication of its results, provided that the information will be anonymous and the name of my child will not be revealed.		
--	--	--

Name of parent or legal guardian:

I agree that my child may participate in the BIO-STREAMS project on site at the clinic/hospital, led by [name and email] at [**date**].

I acknowledge that my child has agreed to participate and as his/her parent/guardian I agree with it. I may withdraw my consent at any time.

Signature of parent or legal guardian:

Place and date:

Signature of the researcher:

Researcher leading the BIO-STREAMS workshop in [country]: Name, Institution, Email.

For researcher only: If parent or legal guardian is not consenting (e.g. because minor has capacity to consent), please indicate why:

.....

Declaration of Consent – Minor



Participation of a minor in the BIO-STREAMS project study:

Child’s name:

Child’s date of birth:

	YES	NO
I understand what this research is about.		
I understand what my role in the research will be, what I will be doing.		
I know what data will be collected about me, and how it will be processed.		
I have been able to ask questions and get answers.		
I am happy to participate in this activity and be part of the research.		
I know that I can withdraw my consent at any time and I know who to contact.		
I agree to participate in the BIO-STREAMS project workshop at [BEN name] led by [PI’s name and email]		
I consent to my personal data being processed for the purposes of the BIO-STREAMS project workshop.		

I consent my personal data to be used for future publication of its results, provided that the information will be anonymous and my name will not be revealed.		
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Signature or equivalent of child:

Place and date:

Signature of the researcher:

Researcher leading the BIO-STREAMS workshop in [**country**]: **Name, Institution, Email.**

For researcher only: If child is not consenting (e.g. because minor has no capacity to consent), please indicate why:

.....

Privacy Notice of [Clinical Partner] - BIO-STREAMS Project



1. Introduction

This Notice explains how [BEN name] processes your or your child's personal data due to your participation in the co-creation workshops of the BIO-STREAMS project, funded within the framework of the Horizon Europe Programme (approval number: 101080718).

2. Personal data we collect about you / your child

The following personal data may be processed throughout the BIO-STREAMS workshops:

- Basic demographic information (e.g. age, gender and school grade)
- Data collected during co-creation workshops from data subjects' responses to questions

3. Purposes of processing and legal bases

Your / your child's personal data is processed for the following purposes:

- To fulfil the purposes of the co-creation workshop, i.e., to gather insights about BIO-STREAMS intervention and the BIO-STREAMS study
- To comply with, and demonstrate compliance with, legal and ethical obligations to which we are subject
- To pseudonymize and anonymize personal data to ensure confidentiality

The lawful basis for processing of personal data is **informed and explicit consent** given by children and/or legal guardians, depending on the capacity of the child to lawfully consent to data processing.

Any such personal data will be processed in accordance with the European General Data Protection Regulation (GDPR, 2016/679). The responsible entity (i.e. controller) for the processing of personal data as part of the study is [BEN name], [**contact details**].

Your data will be stored at [BEN] for [**X period**].

4. Your privacy rights

You / your child have data protection rights, including the right to access your / your child's Personal Data, the right to obtain a copy of such Personal Data, to request rectification, deletion or restriction of processing, to withdraw your consent the processing, to transfer it to another data controller.

Participants also have the right to lodge a complaint or seek remedial measures with the supervisory authority [***name of authority in the country***].

5. How to contact us to exercise your rights

If you wish to contact us and/or exercise the rights listed above, you may submit a request by contacting: [***List contact details for privacy contact at partner here***]

6.11 Intervention Study Materials

Appendix 7: Consent form Package for the Intervention Study

Information on consent forms and letters for co-creation workshops (Appendix 6) and the intervention study might differ. This is because intervention study is being prepared several months after the co-creation workshops and new information regarding data handling and privacy has been added to the letters and texts adapted accordingly.

BIO-STREAMS Pilot Information Letter to Parents/Guardians and Competent Children

[Actual Date]



Introduction

We are inviting you (or your child) to take part in the BIO-STREAMS project, which aims to help children, their peers, and families to maintain a healthy lifestyle through education and digital tools. BIO-STREAMS also aims to facilitate and conduct scientific research on childhood obesity based on data collected from children with and without obesity across the EU. Central to this effort is the creation of a pan-european virtual biobank that enables us, and our partners, to share valuable information without compromising patient confidentiality.

As you may be aware, overweight and obesity rates have reached epidemic proportions across the EU and continue to grow. Innovative solutions are required to prevent, improve, and better understand this phenomenon. The BIO-STREAMS project is primarily dedicated towards understanding genetic and environmental causes of obesity and excess weight, and whether digital tools like apps and games can improve children's and adolescents' health. Early-age interventions are known to be a key piece of this puzzle, potentially having long-term beneficial outcomes for health throughout life, which is why we are focusing on children under the age of 18.

Before you decide whether to participate and sign the consent form, or allow your child to do so, please take your time to read this information letter. If you have any questions, we are here to help and would be happy to provide more detail (see section below for contact information). Your understanding and comfort with the study are essential.

Who are we?

We are a team of researchers from [**BEN name**] working under the European Union Horizon Europe Program funded project, BIO-STREAMS (*Multi-Pillar Framework For Children Anti-Obesity Behaviour Building On An EU Biobank, Micro Moments And Mobile Recommendation Systems, Approval Number 101080718*).

The project brings together 29 partners from 15 European countries, with a shared goal of improving children's health and preventing obesity through science, education, and technology.

BIO-STREAMS includes experts from many fields – such as healthcare, technology, education, law, and project management – and our team at [organization] is one of the seven research centers running clinical activities in Belgium, Bulgaria, Greece, Spain, Sweden and Slovenia.

For this study, we at [BEN name] will be your main point of contact. If you have any questions or concerns, please don't hesitate to reach out to us. Our team is led by [PI Name] and you can reach us using this e-mail address: [PI email].

What does the study involve?

We are recruiting children and adolescents aged 5-18, both with and without overweight or obesity, to participate in the study. Participation will help us better understand how personal health, lifestyle behaviours, and genetic factors influence long-term health, and whether personalised digital recommendations can make a difference.

If you choose to take part, you (or your child) will be asked to:

- Provide health-related information through questionnaires and interviews,
- Allow access to existing medical records already held by [BEN name],
- Provide biological samples, including saliva at the start and end of the study, and in some cases, a blood sample (if recent results are not already available),
- Participate in a 4-month lifestyle intervention, supported by a mobile app that offers personalized recommendations about physical activity and nutrition based on each child's needs and preferences.

Throughout the intervention, we will check how participants are engaging with the recommendations and collect follow-up data to assess any changes in health behaviors or well-being.

At the end of the study, we will again collect saliva and ask participants to complete questionnaires. This will allow us to evaluate the impact of the digital tool and identify whether changes in health markers or behaviors have occurred.

Benefits of Participation

Whilst the main benefits of the project are the betterment of public health, and the improvement of scientific knowledge, you and your child may benefit from personalized interventions relating to health. You and your child may also gain from improved understanding of health-related behaviors. No compensation will be provided.

Risks and Discomforts of Participation

Taking part in the study involves minimal risks, but there are a few things to be aware of. Some participants may experience mild discomfort during the collection of biological samples, such as saliva or—if needed—a blood sample. These procedures are performed according to standard clinical guidelines to ensure the safety of participants and, if necessary, facilitate referrals to clinical specialists.

You (or your child) may also find some topics—such as body weight, eating habits, or physical activity—sensitive or emotionally uncomfortable. This is entirely understandable. All

discussions will be conducted in a respectful and age-appropriate way, and children may stop or pause their participation at any time, without any explanation or consequence.

If needed, psychological support will also be made available.

In addition, as with any research project that involves the processing of personal data, there is a risk of a data breach. We are committed to protecting your privacy and have implemented strict confidentiality protocols and security measures to minimise this risk.

Return of Results

If, during the course of the study, we discover any health-related findings that could impact your child's well-being, we will inform you (as the legal guardian) and, if necessary, provide medical guidance. You may also choose whether or not to receive such findings at the beginning of the study.

Privacy and Confidentiality

The study involved the collection and use of sensitive personal data, including health, behavioural, and genetic information. To protect your (or your child's) privacy, all information collected about you (or your child) will be kept strictly confidential and handled according to the General Data Protection Regulation (GDPR). Participation in the study is based on informed and explicit consent, which can be withdrawn at any time.

All data collected will be processed within the EU, using secure systems and encryption. Only the minimum data necessary for the study will be accessed, and only by authorised staff. Each participant will be assigned a pseudonymized study code, and identifying information (such as names or addresses) will be stored separately and securely. Only the local clinical team will be able to link this code back to an individual, if necessary to honour participants' rights (e.g. withdrawal).

Although [organization] is primarily responsible for handling your personal data, other institutions that are involved with BIO-STREAMS may access and use personal data in accordance with the Privacy Notice below. No other institutions will be given access to you (or your child's) personal data. If you have any questions about your privacy, please contact [organization].

Once the study concludes, anonymised data (with personal identifiers removed) may be used for further research and shared with policymakers and researchers to support child health initiatives. All published or shared data will be fully anonymised or aggregated, ensuring no individual can be identified.

Voluntary Participation

Participation in the study requires informed consent and is completely voluntary. This means that you agree to the collection and use of your (or your child's) personal information for the purposes of the workshop. However, if you decide not to take part, it will not affect your child's access to healthcare or other services in any way, and there will be no penalty.

Consent must be provided by a legal guardian for all participants under the legal age of consent. In addition:

- Children who are old enough to understand the study will also be asked to give their own assent.

- Adolescents (e.g. aged 12 and above, depending on national law) will be invited to co-sign the consent form, alongside their parent or guardian, to confirm their willingness to participate.
- If a child is not old enough to give informed assent, we will still explain the study in an age-appropriate way.

If at any time your child expresses that they do not wish to continue participating, their decision will be respected, even if you have previously given consent.

Withdrawal

You (or your child) have the right to withdraw consent at any time, either fully or partially. This includes the right to:

- End participation in the study,
- Stop sharing certain types of data,
- Request collected data to be deleted.

To do so, simply inform the study team using the contact details provided. You do not need to give a reason.

Contact Details

If you would like more information, you may call us. You are welcome to call us at any time before or during the study, with questions and/or concerns, or if you would like to withdraw yourself or your child from the study. You can contact [insert contact details here].

Conclusion

We very much appreciate your consideration in participating in BIO-STREAMS, which we hope will have a meaningful impact on public health and scientific research. If you agree to participate, or to your child's participation, please read and sign the consent form(s) below. Depending on age, we may require the consent of both a legal guardian/parent and the child, or just one.

BIO-STREAMS Simplified Information Letter

[*Actual Date*]



Hello!

We're inviting you to join a project called **BIO-STREAMS**. This project is all about helping you, your friends, and your family to stay healthy and happy. We use fun digital tools and games to teach you about good habits. We're also doing some important research to learn more about why some kids struggle with their weight.

You might have heard that a lot of people, including kids, are having trouble with weight. We're trying to find new ways to help. We think that helping kids when they're young can make a big difference for their whole life.

Before you decide to join us, please read this letter carefully. If anything is unclear, just ask! We're happy to explain.

Who are we?

We're a group of researchers from [*BEN name*], and we're working together with teams across 15 countries in Europe. Our goal is to learn more about how health, habits, and even genes play a role in staying healthy.

If you have questions at any point, you can reach our team lead [*PI*] at [*PI contact details*].

What will you do in the study?

If you join the study, here's what will happen:

- We'll collect some information about your health through questions, surveys, or interviews.
- We may look at medical records we already have at [*BEN name*] (only with your and your parent's permission).
- We'll collect a saliva sample (by a cheek swab) at the start and again at the end. In some cases, we may ask if it's okay to take a blood sample—but only if we don't already have that information.
- You'll use a mobile app for 4 months. The app will give you tips about eating healthy and staying active.

At the end, we'll ask you some questions again and collect another saliva sample to see how the app helped.

What's good about joining?

The main goal of our project is to help everyone stay healthy and to learn more about science. But you might also learn some new things about staying healthy and develop good habits.

Are there any risks?

For the most part, the study is safe and easy. But there are a few things to know. You might feel a little uncomfortable when we collect the saliva sample, and if we take a blood sample. Some questions we ask might feel a little personal or bring up emotions. If anything makes you feel uneasy, please tell us or talk to your parents. We have trained staff who will listen and support you, and if you need more help, we can connect you with someone who can provide it.

Because we collect information as part of the study, there's a small chance that someone could access your data when they shouldn't — but we do everything we can to stop that from happening. There's also a chance that we learn something unexpected about your health. If that happens, we'll let your parent or guardian know and, if needed, help them get advice from a doctor. You and your family can also decide whether or not you want to receive this kind of health information.

But don't worry, we're doing everything we can to keep you safe. We'll offer support if you need it, we have strict rules about keeping your information private, and you can leave the study at any time if you want to.

What about my privacy?

We promise to keep all your personal and health information private and safe. We follow all the rules, including the General Data Protection Regulation (GDPR). We might share some information with other people working on BIO-STREAMS, but we'll remove any details like your name, address, and birth date. Only we at [**BEN Name**] will be able to identify you directly from the information we might share.

Do I have to join?

Joining the study is totally up to you. You can say no or leave the study at any time, and it won't affect anything else, like your health.

What about consent?

Before you can join the study, we need to make sure you're okay with it — and that your parent or guardian is too.

If you're old enough to understand what the study is about, we'll talk to you and ask if you'd like to take part. We'll also ask your parent or guardian to give permission by signing a form.

If you're a bit younger, we'll still talk to you about the study and make sure you're okay with joining, even though your parent or guardian will make the final decision. If you're not sure or don't want to join, that's completely fine — we'll always listen to how you feel.

And if you or your parent or guardian ever change your mind after saying yes, you can stop at any time.

Need more information?

If you want to know more, you can call us anytime, whether you have questions, concerns, or if you want to leave the study. Or you can ask your parent or guardian to do so for you. You can contact us at [**insert contact details here**].

Thank you!

We really appreciate you thinking about joining BIO-STREAMS. We hope this project will make a big difference for everyone's health. If you want to join, please read and sign the consent form below.

Declaration of Consent – Parent or Legal Guardian



Participation of a minor in the BIO-STREAMS project study:

Child’s name:

Child’s date of birth:

	YES	NO
I understand what this research is about.		
I understand what my child’s role in the research will be, what they will be doing.		
I know what data will be collected about my child, and how it will be processed.		
I have been able to ask questions and get answers.		
I am happy for my child to participate in this activity and be part of the research.		
I know that I can withdraw my consent at any time and I know who to contact.		
I agree that my child may participate in the BIO-STREAMS pilot study at [BEN name] led by [PI name and email] at [date].		
I consent to my child’s personal data being processed for the purposes of the BIO-STREAMS project research.		

Name of parent or legal guardian:

Signature of parent or legal guardian:

Place and date:

Signature of the researcher:

Researcher leading the BIO-STREAMS workshop in [**country**]: **Name, Institution, Email.**

For researcher only: If parent or legal guardian is not consenting (e.g. because minor has capacity to consent), please indicate why, and any further relevant details:

.....

Declaration of Consent – Minor



Participation of a minor in the BIO-STREAMS project study:

Child’s name:

Child’s date of birth:

	YES	NO
I understand what this research is about.		
I understand what my role in the research will be, what I will be doing.		
I know what data will be collected about me, and how it will be processed.		
I have been able to ask questions and get answers.		
I am happy to participate in this activity and be part of the research.		
I know that I can withdraw my consent at any time and I know who to contact.		
I agree to participate in the BIO-STREAMS project workshop at [BEN name] led by [PI name and email] at [date] .		
I consent to my personal data being processed for the purposes of the BIO-STREAMS project research.		

Signature or equivalent of child:

Place and date:

Signature of the researcher:

Researcher leading the BIO-STREAMS workshop in [*country*]: **Name, Institution, Email.**

For researcher only: If child is not consenting themselves (e.g. because minor has no capacity to consent), please indicate why, and any relevant details:

.....

Privacy Notice of [*Clinical Partner*] - BIO-STREAMS Project



1. Introduction

This Notice explains how [**BEN name**] processes your or your child's personal data due to your participation in the BIO-STREAMS project, funded project within the framework of the Horizon Europe Programme (approval number: 101080718).

2. Personal data we collect about you / your child

The following personal data may be processed throughout the BIO-STREAMS project:

- Information establishing identity (e.g. name, surname, address, date of birth) and contact details
- Historical medical information from existing and future records
- Medical information from blood sample
- Data collected through participants' use of BIO-STREAMS mobile applications, including data related to health
- Data collected during recruitment and follow-up, including data related to health
- Genetic data derived from saliva samples

3. Purposes of processing and legal bases

Your / your child's personal data is processed for the following purposes:

- To give recommendations related to nutrition and physical activity through use of BIO-STREAMS mobile applications
- To establish the BIO-STREAMS biobank
- To facilitate medical research
- To comply with, and demonstrate compliance with, legal and ethical obligations to which we are subject
- To pseudonymize and anonymize data to ensure patient confidentiality

The legal basis for processing personal data is **informed and explicit consent** given by children and/or legal guardians, depending on the capacity of the child to lawfully consent to data processing.

Any such personal data will be processed in accordance with the European General Data Protection Regulation (GDPR, 2016/679). All personal data will be stored within the EEA, with appropriate and state-of-the-art security measures.

4. Organizations that process personal data

The main entity responsible for the processing of you or your child's personal data as part of the study is [**BEN name**], [**contact details**].

However, as this is a joint study with other research institutions and technical partners to help facilitate the BIO-STREAMS Project, other research institutions may jointly determine the purposes and means of processing personal data (except personal identifiable information), and process that data (in pseudonymized form) to achieve the abovementioned purposes (and therefore be joint controllers). These other institutions are members of BIO-STREAMS clinical team: UKCM, NKUA, KI, BLOCKS, VHIR, CHUL, PENTELI.

These institutions may also engage other institutions within the BIO-STREAMS project to process personal data on their behalf (i.e. as processors, e.g. UM, HUA, ICSS, ÉONgenetics, AINIGMA, CSCY, TMA, VILABS, UOI, I2GROW, D.TSAKALIDIS-G.DOMALIS, SPHYNX, UKEMED, UKEMED, TECREANDO)

If you would like more information about these institutions and their involvement in BIO-STREAMS, please ask [**Researcher**] at [**contact details**].

5. How we store and share your / your child's personal data

Your / your child's personal data will be stored in a database located at [**PARTNER, ADDRESS**]. This is a secure facility, meeting international security and safety standards. Also, in order to keep your information confidential, numerous safeguards are in place. In particular, we will:

- remove personal identifiers such as your name or date of birth from your samples and records;
- assign codes to your samples and records;
- use stringent security measures to prevent unauthorized use, including strict access controls, and computer security techniques including encryption;
- hold information in secure databases, which can be accessed only by authorized staff members and by approved researchers, who will only have access to coded information; and
- have a decoding step that will allow us to re-link personal details with your samples and information, should you or your child wish to withdraw from the study, access personal data, or to ensure that the data is accurate.

6. How long we store your personal data.

We will retain your Personal Data for as long as necessary to fulfill the purposes for which it was collected. The retention of personal data will be revisited iteratively by the panel of experts, established as part of the Information Management System (IMS), no less than every five (5) years after the completion of the BIO-STREAMS project.

For the specific purposes of establishing the BIO-STREAMS virtual biobank, only anonymized data will be used, ensuring that no link is retained between the data and any individual. This will protect the identity of participants and allow for continued use of the data in research without compromising privacy.

If you or your child wish to exercise the right to be forgotten or withdraw consent, personal data will be removed or anonymized upon request, in accordance with applicable data protection laws. Throughout the process, appropriate technical and organizational measures will be implemented to safeguard your or your child's rights and freedoms.

7. Your privacy rights

As a participant in the BIO-STREAMS project, you / your child have the following data protection rights under applicable privacy laws:

- You have the right to access your (or your child's) personal data and obtain a copy of it.
- You can request the correction of any inaccurate or incomplete personal data.
- You have the right to request the deletion of your (or your child's) personal data, where it is no longer necessary for the purposes for which it was collected.
- You can request the restriction of processing of your (or your child's) personal data under certain conditions.
- You can withdraw your consent for the processing of your (or your child's) personal data at any time.
- You can request the transfer of your (or your child's) personal data to another data controller, where technically feasible.

In addition, participants have the right to lodge a complaint with the relevant supervisory authority in your country, should you feel that your data protection rights have been infringed upon.

[Name of Supervisory Authority in the country] is the designated authority to oversee privacy matters in your jurisdiction.

8. How to contact us to exercise your rights

If you wish to contact us and/or exercise the rights listed above, you may submit a request by contacting: **[List contact details for privacy contact at partner here]**.

7 Appendix B: Recruitment Strategy

The BIO-STREAMS clinical pilot study implements a multi-phase recruitment designed to ensure appropriate participant distribution across all study sites while maintaining ethical standards and scientific validity. Each pilot site will aim to recruit 150 participants, with equal distribution across the three cohorts: 50 children without overweight/obesity (CWO), 50 children with overweight/obesity with normal metabolic parameters (CONM), and 50 children with overweight/obesity with metabolic abnormalities (COMA). All age groups (5-18 years old) should be roughly equally represented, with efforts made to ensure gender balance, though accommodating the naturally higher prevalence of obesity among boys in European populations is acceptable.

7.1 Recruitment Strategy

7.1.1 Phase 1: Building a List of Interested Participants/Families

Recruitment will utilize multiple complementary strategies to identify potential participants:

Clinician Referrals: Medical professionals at each pilot site will identify and recommend families from their patient populations who are likely to be responsive and engaged in the study. This hand-picking approach by doctors is particularly valuable for identifying well-matched participants.

Passive Recruitment: Information materials including leaflets (Figure 10, Figure 11) with QR codes, digital content on hospital screens, video presentations explaining the participant journey, and articles in hospital magazines will be used to raise awareness of the study.

Internal Dissemination: Each pilot site will leverage internal communications channels to inform healthcare staff about the study, enabling broader identification of potential participants.

Direct Outreach: Where appropriate, mailing lists will be used to contact existing patients with information about the study opportunity.

Co-creation Workshop Participants: Families who participated in the earlier co-creation workshops will be invited to join the intervention study, leveraging their existing familiarity with the project goals.

Outside BioBank

Data collected in the study will be stored locally in our servers within a so-called 'data-hub' that will be part of a European-wide BIO-STREAMS BioBank. The purpose of such BioBank is to offer a decentralized data management system. All participant data will be pseudonymized and unidentifiable.

Get in touch with us to enrol!

The study is conducted by [name of pilot site]

If you have any questions or wish to enrol, please reach out to the team:

- info@bio-streams.eu
- info@bio-streams.eu
- info@bio-streams.eu

www.bio-streams.eu

BIO-STREAMS

A Multi-Pillar Framework to address childhood obesity by building on an EU biobank, micro-moments and mobile recommendation systems

Biosampling

Data collected in the study will be stored locally in our servers within a so-called 'data-hub' that will be part of a European-wide BIO-STREAMS BioBank. The purpose of such BioBank is to offer a decentralized data management system. All participant data will be pseudonymized and unidentifiable.

[@BioStreams_EU](#)
[@bio-streams](#)
[bio-streams.eu](#)

Funded by the European Union
 Project funded by the Austrian Government
 Project funded by the Hungarian Government
 Project funded by the Slovak Republic
 Project funded by the Slovenian Government
 Project funded by the Spanish Government

The Study

What is the aim of the study?

The scientific study aims to evaluate the effectiveness of a personalized intervention for tackling childhood and adolescent overweight and obesity.

The intervention includes recommendations for a healthy lifestyle (e.g., personalized nutrition plans and physical activity) supported by healthcare professionals.

The programs are accessible through an interactive online platform where children and/or parents can log various daily metrics (e.g., food intake, step count, mood, screen time, family time, etc.). The platform also features fun games that teach children to make healthier food choices, stay active, and develop beneficial habits.

The study will be conducted in seven clinical centres across six European countries: Bulgaria, Belgium, Sweden, Slovenia, Greece, and Spain.

Figure 10: Recruitment Leaflet Designed for The Study, Part 1.

Inside

WHO can participate?

- Children and adolescents aged 5 to 18 years.
- They must have access to a smartphone or tablet (or a parent must provide a device).
- They need to meet specific clinical criteria related to weight – the attending physician or principal investigator will determine if the child is eligible to participate in the study.

WHY participate?

- Your child will develop long-lasting healthy habits in a fun and interactive way.
- You will contribute to the fight against childhood obesity at a European level.
- You will gain free access to innovative, digital, and personalized health tools.

What does participation include?

Use of the BIO-STREAMS platform for healthy lifestyle recommendations: a 4-month digital intervention with targeted recommendations for nutrition and physical activity

Ethical aspects

- The study has been approved by ethical committees and complies with GDPR requirements.
- There is no financial compensation.

Digital intervention

The intervention will be delivered through the ActiveHealth app that has been developed within the project. The app will include personalized recommendations regarding healthy lifestyle - diet and physical activity, daily logs of lifestyle habits, progress tracking in multiple categories, and micro-moments to stimulate healthy behaviour.

To keep children engaged, the app includes links to serious games also developed by the project team. The games include a quiz teaching healthy facts, educational 'Food ninja' game, and an exergame 'Let's move' with physical exercises.

Figure 11: Recruitment Leaflet Designed for The Study, Part 2.

7.1.2 Phase 2: Initial Screening of Families

Once a preliminary list of potential participants is established, sites will conduct a thorough screening process:

Eligibility Assessment: Research staff will verify that potential participants meet all inclusion criteria and have none of the exclusion criteria listed in the protocol.

Communication Methods: Sites may use phone calls, video conferences, or in-person conversations during regular clinical visits to assess family interest and eligibility.

Collaborative Approach: Researchers and clinicians will work together to identify the most suitable participants, with clinicians providing valuable insights into family dynamics and potential engagement levels.

Group Assignment: Based on anthropometric measurements and metabolic parameters, participants who meet inclusion criteria will be assigned to the appropriate cohort (CWO, CONM, or COMA).

7.1.3 Phase 3: Formal Enrollment

Once eligibility is confirmed and initial interest is established:

Informed Consent: Families will receive comprehensive information about the study, and signed consent forms will be collected according to local legal requirements, with appropriate consent/assent procedures for different age groups.

Data Collection: Baseline data will be collected according to the protocol specifications and entered the study database following the data model established in Work Package 3.

Cohort Confirmation: Final assignment to cohorts will be confirmed based on comprehensive assessment of the participants' clinical profiles.

7.1.4 Special Considerations

Recruitment Adaptation: Strategies may vary between centers based on their patient populations. For example, obesity centers like CHUL may need different approaches for recruiting CWO participants compared to CONM and COMA groups.

Active Retention: Throughout the recruitment and study period, sites will maintain ongoing communication with enrolled families to minimize dropout rates and ensure continued engagement.

Monitoring: Recruitment progress will be regularly monitored across all sites, with reports at months 11 and 18 of the project to track progress toward enrollment targets.

The recruitment approach emphasizes transparency, ethical considerations, and scientific rigor while acknowledging the practical challenges of recruiting across diverse clinical settings.

This carefully structured process aims to ensure the study achieves its required sample size with appropriate distribution across cohorts, age groups, and genders.

8 Appendix C: Standard Operating Procedures for the Prospective Study



Standard Operating Procedures for the Prospective Study: Data Monitoring and Adverse Effects Management

Revision: v.1.0

Work package	WP6
Document lead	UKCM, UM
Version	1.0
Authors	Ana Rehberger, Izidor Mlakar

Abstract	This document establishes a comprehensive framework for monitoring data-related adverse effects within the Bio-Streams consortium. The protocol is design as a necessary activity to support execution of Prospective Study. It implements a multi-tiered monitoring structure that integrates expertise from clinical, technical, and ethical domains through a carefully designed committee system. The core committee includes the Coordinator (ICCS), the Clinical Manager (UM), the Regulatory & Ethics Manager (WLC), and the Scientific and Technical Manager (HUA). The committee is further supported by PIs of the clinical sites and External Advisory Board of international experts in nutrition, paediatrics, and global health. This document details Standard Operating Procedures (SOPs) for adverse events monitoring, data access monitoring, transfer supervision, and security incident management, while establishing clear reporting hierarchies and decision-making processes.
Keywords	standard operating procedure, adverse effect monitoring, data management

DOCUMENT REVISION HISTORY

Version	Date	Description of change	List of contributor(s)
1.0	04.12.2024	Initial draft of the SOP	Izidor Mlakar
1.1	13.01.2025	Review of the initial version of the SOP	All partners
2.0	17.02.2025	Application of suggested changes, final version	Izidor Mlakar, Ana Rehberger

Disclaimer

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Project co-funded by the European Commission in the Horizon Europe Programme		
Nature of the document	Standard Operating Procedure	
Dissemination Level		
	SENSITIVE, CONFIDENTIAL	X

TABLE OF CONTENTS

<u>1. GENERAL INFORMATION</u>	151
<u>1.1 Purpose of the Protocol</u>	151
<u>1.2 Scope of the Protocol</u>	151
<u>1.3 Roles and Responsibilities</u>	152
<u>2. REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE CLINICAL COORDINATOR</u>	154
<u>2.1 “Serious adverse event”</u>	154
<u>2.1.1 ‘Adverse event’</u>	154
<u>2.1.2 “Serious adverse event”</u>	155
<u>2.2 Severity assessment</u>	155
<u>2.3 Timelines</u>	156
<u>2.3.1 Immediate reporting and follow-up report</u>	156
<u>2.3.2 Non-immediate reporting</u>	156
<u>2.3.3 Start and end of reporting serious adverse events to the sponsor</u>	156
<u>2.4 Determining causality</u>	156
<u>2.5 Foreseen workflow of reporting of adverse events</u>	159
<u>3. REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE BIO-STREAMS SOP COMMITTEE</u>	160
<u>4. REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE INVESTIGATORS</u>	160
<u>4.1 “Adverse reactions”</u>	160
<u>5. ADVERSE EVENTS REPORTING IN VARIOUS STUDY PHASES AND MODES</u>	160
<u>5.1 Recruitment</u>	160
<u>5.2 Study execution</u>	161
<u>Appendix</u>	161
<u>Adverse Events Report Form</u>	161

8.1 GENERAL INFORMATION

8.1.1 Purpose of the Protocol

This Standard Operating Procedure (SOP) outlines the definition of an adverse and serious adverse event and the reporting structures for adverse and serious adverse events for people participating in BIO-STREAMS Feasibility Study of the Personalized Recommendation System for Obesity Prevention: A Mixed Methods Study (Study 2).

This SOP also describes the procedures study personnel will use to fulfil the regulatory and ethical responsibilities to identify, classify and report adverse events. Researchers should familiarize themselves with the entire contents of this SOP. However, the document is primarily designed as a practical reference guide to be used alongside the study protocol with guidance and oversight by local site Principal Investigators and the clinical coordinator within the BIO-STREAMS study.

This SOP was drafted following the Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') document. More information on the legal basis of adverse event reporting can be found in the mentioned document.

8.1.2 Scope of the Protocol

The protocol's scope is not covering only the technical aspects of data monitoring, but also the human and organizational dimensions that enable implementation of an effective oversight. This protocol applies to all personnel in contact with study participants and all personnel involved in the collection, handling, processing, and transfer of sensitive data related to the prospective study.

8.2 Roles and Responsibilities

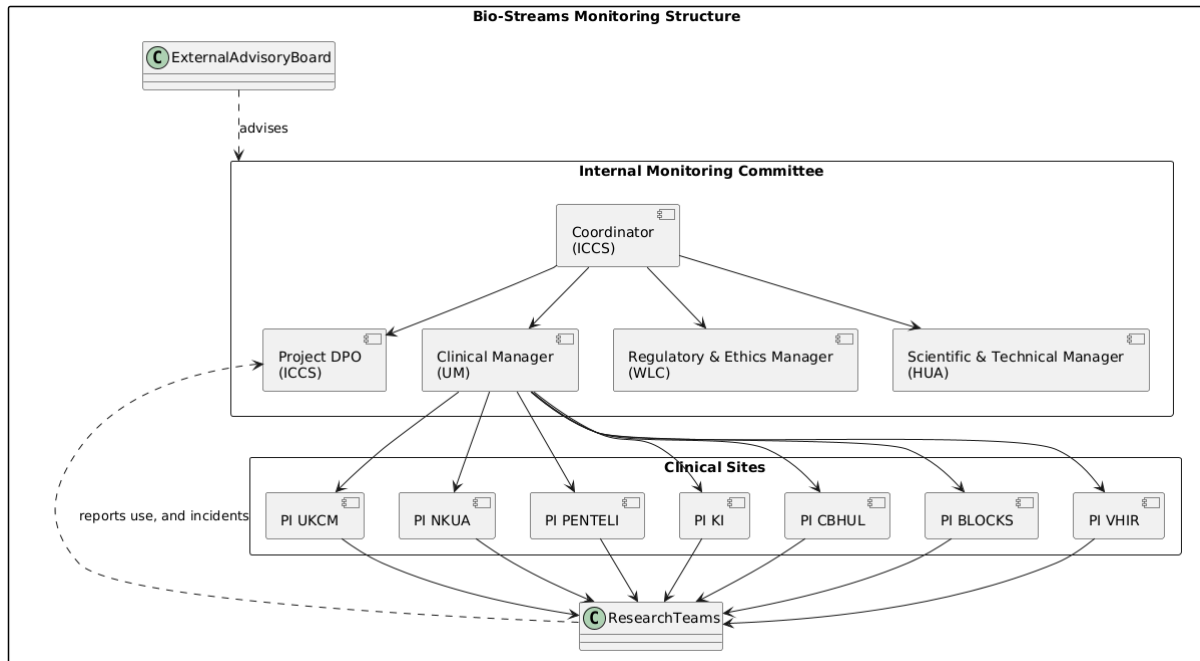


Figure 1: The Monitoring Structure in Bio-Streams

Project’s Data Protection Officer (pDPO): Responsible for overseeing compliance with data protection regulations, conducting risk assessments, and coordinating incident response efforts.

Research Team Members: Required to adhere to the protocol's guidelines for data handling and reporting any suspected adverse events immediately. This includes technical personnel implementing technical safeguards, monitoring systems for unauthorized access, and maintaining logs of data transfers (on the targeted systems).

The BIO-STREAMS SOP Committee: Consists of: the Coordinator (ICCS), the Project’s Data Protection Officer (ICCS), the Clinical Manager (UM), the Regulatory & Ethics Manager (WLC), and the Scientific and Technical Manager (HUA). The committee is further supported by Principal Investigators of the clinical sites (UKCM, NKUA, PENTELI, KI, CHUL, BLOCKS and VHIR)

The **Coordinator’s role** as Committee Chair ensures that monitoring processes remains practical and implementable, while the **Scientific and Technical Manager’s** and **Clinical Manager’s** oversight guarantees that these processes serve rather than hinders research objectives. The **Regulatory & Ethics Manager’s** involvement ensures that all monitoring activities align with ethical principles and legal requirements.

The **Principal Investigators (PIs)** at clinical sites function as main figures in the data monitoring framework, ensuring local data integrity and establishing links in the consortium's broader data oversight chain. Their role encompasses multiple layers of responsibility, starting with the fundamental oversight of data quality and completeness at their respective sites. The

PIs serve as the first line of defense in data protection, taking immediate action when incidents occur and implementing necessary corrective measures, while maintaining clear communication channels with both their local teams and the BIO-STREAMS SOP committee. Beyond their local oversight, PIs participate actively in the consortium's broader monitoring structure through regular committee meetings, status reporting, and direct collaboration.

External Advisory Board members actively contribute to shaping monitoring practices that reflect real-world research needs and challenges. Their involvement ensures that monitoring procedures remain relevant to the scientific goals while meeting international standards of research governance.

Table 1: Persons involved in the BIO-STREAMS SOP Committee

Role	Name and surname	Institution	e-mail
CO	Eleftheria Vellidou	ICCS	ebel@biomed.ntua.gr
DPO	Dimitrios Kalogeras	ICCS	dkalog@gmail.com
CM	Izidor Mlakar	UM	Izidor.mlakar@um.si
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PI-BLOCKS	Radka Savova	BLOCKS	savova.radka@gmail.com
PI-CHUL	Caroline Gernay	CHUL	Cgernay@chuliege.be
PI-KI	Billy Langlet	KI	Billy.langlet@ki.se
PI-NKUA	Evangelia Charmandari	NKUA	evangelia.charmandari@gmail.com
PI-PENTELEI	Georgios Gkritzelas	PENTELEI	gggrtzi@gmail.com
PI-UKCM	Martin Bigec	UKCM	Martin.bigec@ukc-mb.si
PI-VHIR	Andreea Ciudin	VHIR	andreea.ciudin@vhir.org

* Note: CO – Coordinator, DPO - Project’s Data Protection Officer, CM - Clinical Manager, R&E - Regulatory & Ethics Manager, S&T - Scientific and Technical Manager, PI - Principal Investigator

Below we list the responsibilities of principal investigators and clinical coordinator within the BIO-STREAMS study’s adverse events reporting and monitoring procedure.

The investigator’s (i.e. pilot site principal investigator) responsibilities entail:

- reporting of serious adverse events to the clinical coordinator (see section 2)
- reporting of certain non-serious adverse events and/or laboratory abnormalities to the clinical coordinator (see section 3)
- reporting of serious adverse reactions to the National Competent Authority and the relevant Institutional Review Board (IRB)/Ethics Committee
- informing the participant about the adverse event they are experiencing and how it will be managed
- informing site’s investigator with the SOP document (specifically, the workflow of reporting, (see section 2.5) and Adverse Event Report Form (see Appendix 1)

The Clinical Coordinator’s (University of Maribor) responsibilities entail:

- recording of adverse events
- reporting of suspected unexpected serious adverse reactions to the consortium and project Ethics Advisory Board
- informing the investigators
- annual safety reporting to the project consortium and project Ethics Advisory Board

The main responsibility of the Clinical Coordinator is monitoring and ensuring all sites adhere to the ethical principles and procedures according to the approved study protocol.

The Clinical Coordinator will arrange for systems and written standard operating procedures to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and following up.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS BY THE INVESTIGATOR TO THE CLINICAL COORDINATOR

8.3.1 “Serious adverse event”

8.3.1.1 ‘Adverse event’

An “adverse event” is defined as follows: “Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment”.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.3.1.2 “Serious adverse event”

A “serious adverse event” is defined as follows: “Any untoward medical occurrence or effect that at any dose

- A) results in death
- B) is life-threatening
- C) requires hospitalization or prolongation of existing hospitalization
- D) results in persistent or significant disability or incapacity, or
- E) is a congenital anomaly or birth defect’

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Some medical events may jeopardize the subject or may require intervention to prevent one of the above characteristics/consequences.

Medical and scientific judgement should be exercised in deciding whether an event is ‘serious’ in accordance with these criteria.

In the Clinical Intervention Study under the scope of the BIO-STREAMS project, no serious adverse events are expected.

8.3.2 Severity assessment

The term “severe” is often used to describe the intensity (clinical severity) of a specific event. This is not the same as “serious”, as defined in Section 2.1.2, which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe. The intensity of an adverse event will initially be assessed according to the following definitions:

Mild: An event easily tolerated by the participant, causing minimal discomfort (e.g., asymptomatic or mild symptoms, diagnostic observations only, no intervention indicated). Not interfering with everyday activities/functioning.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities. Minimal, local or non-invasive intervention indicated.

Severe: An event that prevents normal everyday activities. Medically significant but not immediately life-threatening. Hospital or prolongation of hospitalization indicated.

8.3.3 Timelines

Adverse events will be reported promptly to the pilot site's principal investigator, the clinical coordinator of the BIO-STREAMS project and relevant IRBs or Ethics Committees. Adverse events reporting will be conducted in accordance with ethical principles of autonomy, beneficence, and non-maleficence, with a focus on minimizing harm to participants. Participants will be informed of any adverse events they experience and provided with information on how they will be managed.

8.3.4 Immediate reporting and follow-up report

Given that no serious adverse events are expected to occur during the study, immediate reporting procedure is not necessary. In case of serious event, study personnel will take immediate steps to address any adverse events reported by participants, including providing medical assistance if necessary.

Participants possibly experiencing serious adverse events will be monitored closely, and appropriate follow-up care will be provided as needed. Participants will be offered support and reassurance throughout the process, including access to counselling or other appropriate support if needed.

8.3.5 Non-immediate reporting

In cases where reporting is not required immediately the investigator will report within 5 to 7 days after the event occurs, taking account of the specificities of the trial and of the serious adverse event. For serious events, the timeline is maximum 48 hours, and a committee should convene in at least 72 hours after the serious adverse event to evaluate the impact of the event on the studies.

8.3.6 Start and end of reporting serious adverse events to the sponsor

The investigator does not need to actively monitor subjects for adverse events once the trial has ended.

8.3.7 Determining causality

Causality of an AE will be assessed in a timely manner, in consideration of the regulatory reporting requirements detailed in Section 2 of this SOP. Causality and expectedness assessments will be carried out by an internal committee that consists of medical investigators of the pilot site team (at least one member per pilot site). Potential adverse events include:

- Physical injury from sports
- Psychobehavioral AEs (anxiety, depression)
- Viral infections
- Allergy reactions
- Weakness and vomiting during the OGTT test (drinking a large amount of dissolved glucose)

- Collapse due to blood sampling (venipuncture)
- Feeling unwell, fatigue, and drowsiness due to occasional hypoglycemia between meals
- The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The above considerations apply also to adverse events occurring in the comparison groups or control groups.

Each Serious adverse event will be classified according to five different levels of causality, which are required when completing and submitting the Adverse Event Report Form. The investigators will use the following definitions in Table 1 to assess the relationship of the serious adverse event to the investigational therapy, intervention procedures for comparators or other study/research procedures.

Table 1. Causality definitions

Causality category	Definition
Definitely not	<p>The relationship to the intervention or research procedures can be excluded when:</p> <ul style="list-style-type: none"> • the event is not a known¹ side effect of the category the intervention belongs to or of similar interventions and procedures. • the event has no temporal relationship with the use of the intervention or the procedures. • the serious event does not follow a known response pattern to the intervention (if the response pattern is previously known) and is biologically implausible. • the discontinuation of intervention or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event. • the event involves a body-site, or an organ not expected to be affected by the intervention or procedure. • the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another intervention, drug, treatment, or other risk factors). <p>In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of intervention/procedures and the serious event.</p> <p>¹ When the event is not a known side effect of the category the intervention belongs to or of similar interventions and procedures, generally is considered “not related”. Yet, the unexpected effect shall not be excluded from evaluation and reporting.</p>

Probably not	The relationship with the intervention seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly	The relationship with the intervention is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another intervention, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible
Probably	The relationship with the intervention seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Definitely	<p>The serious event is associated with the intervention or with procedures beyond reasonable doubt when:</p> <ul style="list-style-type: none"> • the event is a known side effect of the category the intervention belongs to or of similar interventions and procedures. • the event has a temporal relationship with intervention or procedures. • the serious event follows a known response pattern to the intervention (if the response pattern is previously known). • the discontinuation of the intervention (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible). • other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another intervention, drug, or treatment) have been adequately ruled out. <p>In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of intervention/procedures and the serious event.</p>

The site’s medical investigators will distinguish between serious adverse events related to the intervention and those related to the study/research procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the intervention. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of intervention.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

2.5 Foreseen workflow of reporting of adverse events

The BIO-STREAMS monitoring procedures are adapted to the specific roles and responsibilities of clinical and technical partners. These procedures ensure secure and efficient data handling while maintaining clear accountability and oversight.

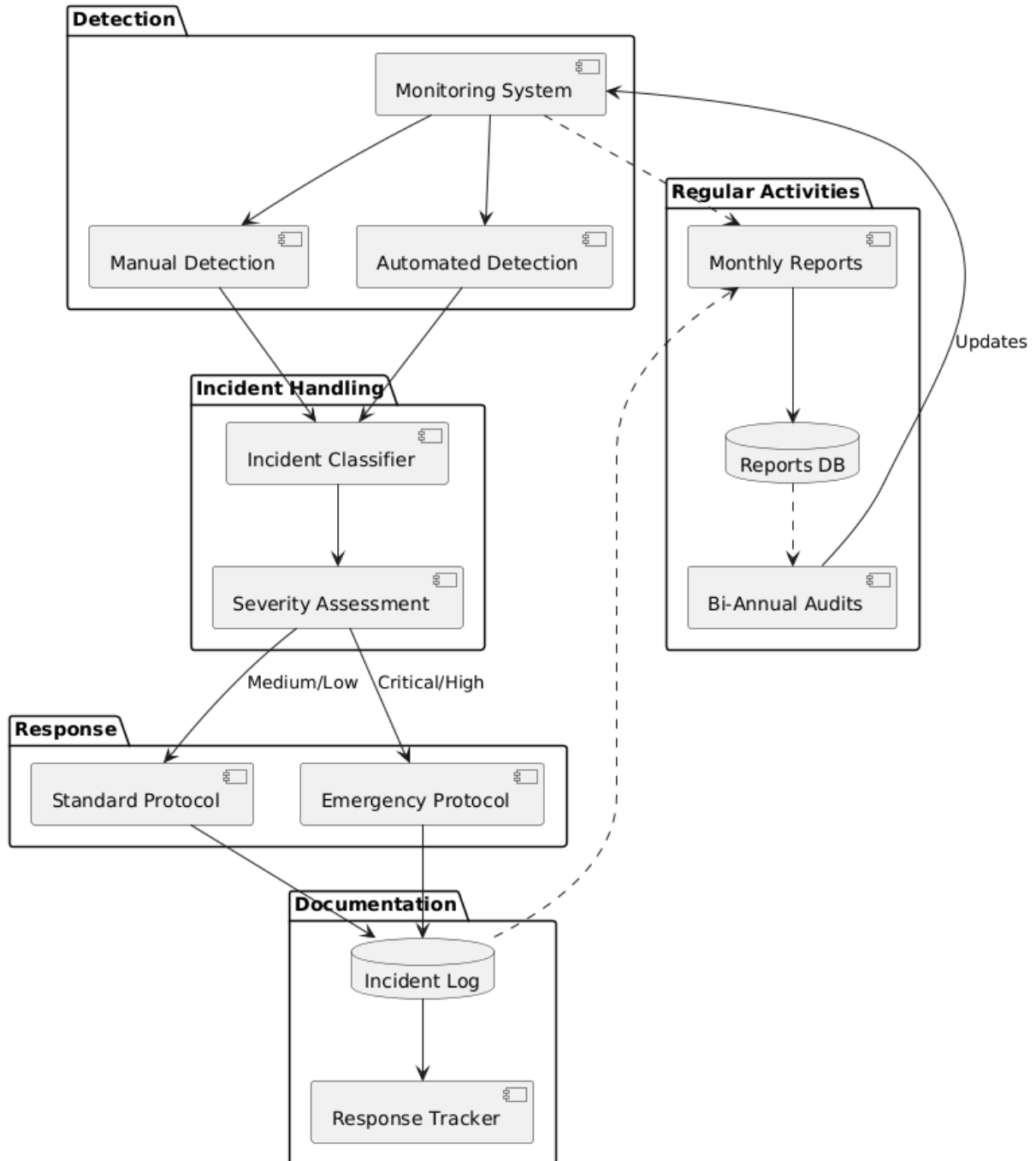


Figure 2: Monitoring Framework

8.4 REPORTING OF NON-SERIOUS ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES BY THE INVESTIGATOR TO THE BIO-STREAMS SOP COMMITTEE

Adverse events and/or laboratory abnormalities identified as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods: 5-7 days for non-serious events and 48 hours for serious adverse events.

8.5 REPORTING OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS BY THE INVESTIGATORS

As no serious events are expected to happen, they will not be reported by the investigators to their respective authorities or BIO-STREAMS SOP committee. If, however, a serious adverse event is confirmed, all investigators will report them to the respective authorities.

8.5.1 “Adverse reactions”

All untoward and unintended responses to an investigational psychological intervention. All adverse events judged by either the reporting investigator or BIO-STREAMS SOP committee as having a reasonable causal relationship (e.g., definitely, probably or possibly related) to a psychological therapy/intervention qualify as adverse reactions.

In the context of BIO-STREAMS study, the following adverse reactions are expected:

- Disappointment (including termination of participation) if the treatment results do not meet the participant's expectations
- Depression due to failure in treatment
- Self-aggressive behavior due to failure in losing weight, etc.

8.6 ADVERSE EVENTS REPORTING IN VARIOUS STUDY PHASES AND MODES

8.6.1 Recruitment

During the recruitment phase the risk for adverse events will be re-evaluated for each perspective participant.

8.6.2 Study execution

During the execution of the study the study personnel will monitor participants for adverse events throughout the duration of their involvement in the study using the following methods of monitoring:

- Regular check-ins: Participants will be asked to report any adverse events during follow-up visits, interviews, or interactions with study personnel.
- Passive monitoring: Monitoring of digital intervention usage data for signs of adverse events, such as increased stress levels or discontinuation of use.
- Adverse event logs: Study personnel will maintain detailed logs of any adverse events reported by participants or observed during the study.

Appendix

Adverse Events Report Form

Hereby, the Adverse Events Report Form overview is appended. The form should be filled in the relevant Excel file to facilitate merging of data into a single record.

Study title: Feasibility Study of a Personalized Recommendation System for Obesity Prevention: A Mixed Methods Study

Reporting to:	BIO-STREAMS SOP Committee
----------------------	----------------------------------

Participating site	
Event reported by (principal site investigator)	
Email address of person completing the form	
Date of the report	
Participant ID	

Adverse event

Unique adverse event reference (form: DDMMYYYY-Pilot site acronym-number of the event in the pilot site)	
Description of event	
Event start date	
Event start time	

Date PI aware of the event	
Time PI aware of the event	
Severity assessment (mild, moderate, severe)	

Actions taken in response (continued with study, discontinued with study)	
---	--

Resolution date of the event	
Resolution time of the event	
Duration of the event	
Participant outcome (resolved, ongoing, unknown)	

Follow-up plan (if not resolved at time of completing form):	
--	--

Seriousness classification

Is this a serious adverse event? (Yes, No)	
If Yes, report to Sponsor within 7 days	
<i>An AE is “serious” if it results in the following: (a) Death; (b) Life-threatening illness or injury; (c) Disability or incapacity (including permanent impairment of a body structure or a body function); (d) Medical or surgical intervention to prevent the above; (e) Requires hospitalization or extends hospitalization; (f) Fatal? distress or death; or (g) Otherwise medically significant. If a serious event has occurred, please write to the right side which type from above.</i>	
Causality of a serious adverse event	

Event narrative

Narrative (e.g. background and context, onset of symptoms, treatment, medications, outcome, reason for causality assessment):	
---	--

Relevant Medical History (e.g. please state any relevant pre-existing conditions):	
--	--

Signatures:	
PI Name:	
PI signature:	
Date:	
BIO-STREAMS SOP Representative:	
BIO-STREAMS SOP Representative signature:	
Date:	

9 Appendix D: Self-report Outcome Measures

General instructions for the questionnaires

Thank you for helping us by filling out the following questionnaires! We want to learn more about your behaviours, thoughts and feelings.

Remember that there are no right or wrong answers! You just have to answer the questions as honestly as you can. When answering a question with a scale of answers, it is okay to choose the lowest or highest point if that is more accurate for your behaviours or the way you feel. You do also not have to answer questions you do not feel comfortable answering, but the more questions you answer, the more helpful it will be to us.

Thank you for your participation - your input is valuable to our research!

Demographic information

1. Sex of a participant:
 - Female
 - Male

2. Age group of a participant:
 - 5-8 years
 - 8-10 years
 - 10-14 years
 - 14 to 18 years

3. Number of siblings: _____

4. Type of school the participant is attending:
 - Private
 - Public
 - Not applicable

5. Education of parent or caregiver:
 - Primary education or less,
 - Lower secondary education,
 - Higher secondary education,
 - Bachelor's degree or equivalent,
 - Master's degree or equivalent,
 - Doctoral degree or equivalent

6. Education of second parent or caregiver (if applicable):
 - Primary education or less,
 - Lower secondary education,
 - Higher secondary education,
 - Bachelor's degree or equivalent,
 - Master's degree or equivalent,
 - Doctoral degree or equivalent

7. Employment status of parent or caregiver:

- full-time,
- part-time,
- unemployed,
- other,
- does not apply

9. Employment status of second parent or caregiver (if applicable):

- full-time,
- part-time,
- unemployed,
- other,
- does not apply

10. Yearly family income: _____

11. Country or region: _____

12. Living location:

- City center
- Suburbs
- Rural

Penn State Worry Questionnaire for Children (PSWQ-C)

Please read each statement and indicate how often it is true for you, by selecting the appropriate number. There are no right or wrong answers; we want your honest thoughts and feelings.

	1	2	3	4	5
	(Not at all true for me)				(Very true for me)
1. I worry about things working out the way I want them to.	1	2	3	4	5
2. Once I start worrying, I can't stop.	1	2	3	4	5
3. I worry about bad things happening to me.	1	2	3	4	5
4. I worry about things that might go wrong.	1	2	3	4	5
5. I worry about other people getting mad at me.	1	2	3	4	5
6. I worry about how well I will do in school.	1	2	3	4	5
7. I worry about getting into trouble.	1	2	3	4	5
8. I worry that I will say or do the wrong things.	1	2	3	4	5
9. I worry about what people think of me.	1	2	3	4	5

10. I worry about not being able to control my worries.	1	2	3	4	5
11. I worry about my family getting hurt.	1	2	3	4	5
12. I worry about things that happened in the past.	1	2	3	4	5
13. I worry about not being as good as other kids my age.	1	2	3	4	5
14. I worry about bad things happening to people I care about.	1	2	3	4	5

Center for Epidemiological Studies Depression Scale for Children (CES-DC₄)

Please read each statement and indicate your degree of agreement by selecting the appropriate number. There are no right or wrong answers; we want your honest thoughts and feelings.

During the past week	Not at all	A little	Some	A lot
1. I was happy	1	2	3	4
2. I felt like the kids I know were not friendly or that they didn't want to be with me.	1	2	3	4
3. I felt sad	1	2	3	4
4. It was hard to get started doing things	1	2	3	4



KIDSCREEN-10 Index

Health Questionnaire for Children and Young People

Child and Adolescent Version 8 to 18 Years

English (US)

Hello,

How are you? How do you feel? This is what we would like you to tell us.

Please read every question carefully. What answer comes to your mind first? Choose the box that fits your answer best and cross it.

Remember: This is not a test so there are no wrong answers. It is important that you answer all the questions and also that we can see your marks clearly. When you think of your answer please try to remember the last week.

You do not have to show your answers to anybody. Also, nobody who knows you will look at your questionnaire once you have finished it.

About Your Health

Thinking about the last week...					
1. Have you physically felt fit and well?	not at all	slightly	moderately	very	extremely
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Have you felt full of energy?	never	almost never	sometimes	almost always	always
	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

3. Have you felt sad?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
4. Have you felt lonely?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
5. Have you had enough time for yourself?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
6. Have you been able to do the things that you want to do in your free time?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
7. Have your parent(s) treated you fairly?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
8. Have you had fun with your friends?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>
9. Have you got on well at school?	not at all <input type="radio"/>	slightly <input type="radio"/>	moderately <input type="radio"/>	very <input type="radio"/>	extremely <input type="radio"/>
10. Have you been able to pay attention?	never <input type="radio"/>	almost never <input type="radio"/>	sometimes <input type="radio"/>	almost always <input type="radio"/>	always <input type="radio"/>

In general, how would you say your health is?

- excellent
- very good
- good
- fair
- poor

WHO-5 Well-being Index

Please respond to each item by marking one box per row, regarding how you felt in the last two weeks.

		All of the time	Most of the time	More than half the time	Less than half the time	Some of the time	At no time
WHO 1	I have felt cheerful in good spirits.	5	4	3	2	1	0
WHO 2	I have felt calm and relaxed.	5	4	3	2	1	0
WHO 3	I have felt active and vigorous.	5	4	3	2	1	0
WHO 4	I woke up feeling fresh and rested.	5	4	3	2	1	0
WHO 5	My daily life has been filled with things that interest me.	5	4	3	2	1	0

Food and Nutrition Literacy (FNLIT)

Please read each statement and indicate your degree of agreement by selecting the appropriate number. There are no right or wrong answers; we want your honest thoughts and feelings.

Knowledge (cognitive domain)	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
1. Consumption of salty snacks (e.g. chips, corn puffs, etc.) is harmful for health	1	2	3	4	5
2. Excessive consumption of sugar, sweets, and chocolate is harmful for health	1	2	3	4	5
3. Consumption of salami and sausage that are high in fat may cause obesity	1	2	3	4	5
4. Consumption of salamis and sausages may cause cancer	1	2	3	4	5
5. Reading of production and expiration date on food package is important for health	1	2	3	4	5

Functional (skills)	Never	Seldom	Sometimes	Usually	Always
6. I eat a variety of vegetables (e.g., lettuce, cabbage, tomatoes, carrots, etc.), every day	1	2	3	4	5
7. I share the nutritional issues that I obtain from various sources with others (e.g., friends, family, etc.)	1	2	3	4	5
8. I talk to my friends and family about healthy eating	1	2	3	4	5
9. If I have any questions about food and nutrition issues, I'm able to get information and advice from parents, teachers, etc	1	2	3	4	5
10. I prepare my own snacks for school	1	2	3	4	5
11. I bring healthy snacks to school	1	2	3	4	5
12. I regularly do exercise or walk for 30 to 40 minutes every day.	1	2	3	4	5
13. I wash and prepare fruits and vegetables myself.	1	2	3	4	5
14. I eat fruits every day.	1	2	3	4	5
15. I eat breakfast every day	1	2	3	4	5

Self-regulation of eating behavior questionnaire (SREBQ)

Please read the following statements and tick the boxes most appropriate to you.

For the next few questions, please, understand that:

- 'Tempting foods' are any food you want to eat more of than you think you should.
- 'Eating intentions' refer to the way you are aiming to eat, for example you may intend to avoid tempting foods or eat healthy foods.

	Never	Rarely	Sometimes	Often	Always
1. I'm good at resisting tempting food					
2. I give up too easily on my eating intentions					
3. I easily get distracted from my eating intentions					
4. I find it hard to remember what I have eaten throughout the day					
5. If I am not eating in the way I intend to I make changes					

Weight Self-Stigma Questionnaire (WSSQ)

Please read each statement and indicate your degree of agreement by selecting the appropriate number. There are no right or wrong answers; we want your honest thoughts and feelings.

	Completely Disagree	Disagree	Nor disagree or agree	Agree	Completely Agree
1. I'll always go back to being overweight.	1	2	3	4	5
2. I caused my weight problems.	1	2	3	4	5
3. I feel guilty because of my weight problems.	1	2	3	4	5
4. I became overweight because I am a weak person.	1	2	3	4	5
5. I would never have any problems	1	2	3	4	5

with weight if was stronger.					
6. I don't have enough self-control to maintain a healthy weight.	1	2	3	4	5
7. I feel insecure about others' opinions of me.	1	2	3	4	5
8. People discriminate against me because I've had weight problems.	1	2	3	4	5
9. It's difficult for people who haven't had weight problems to relate to me.	1	2	3	4	5
10. Others will think I lack self-control because of my weight problems.	1	2	3	4	5
11. People think that I am to blame for my weight problems.	1	2	3	4	5
12. Others are ashamed to be around me because of my weight.	1	2	3	4	5

Perceived Research Burden Assessment (PeRBA)

The purpose of this form is to help us understand your views about participating in a research study. As you read each statement, please circle the response that best describes how you feel about the research study that you just heard about.

Dimension: Psychological burden	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1. I feel that the researchers might ask me too many questions	1	2	3	4	5
2. I feel that the researchers might ask me questions that are too personal	1	2	3	4	5
3. I feel that the researchers might call or contact me or my family members too often	1	2	3	4	5

4. I feel that my personal information might not be kept private	1	2	3	4	5
5. I feel that I may become emotionally upset by the research procedure(s)	1	2	3	4	5
6. I feel that I may have second thoughts about my decision to participate in this study	1	2	3	4	5
7. I feel that I may regret my decision to participate in this study	1	2	3	4	5

User Experience (UEQ-S) – Short version

Please make your evaluation now.

For the assessment of the product, please fill out the following questionnaire. The questionnaire consists of pairs of contrasting attributes that may apply to the product. The circles between the attributes represent gradations between the opposites. You can express your agreement with the attributes by ticking the circle that most closely reflects your impression.

Example:

attractive	○	<input checked="" type="radio"/>	○	○	○	○	○	unattractive
-------------------	---	----------------------------------	---	---	---	---	---	---------------------

This response would mean that you rate the application as more attractive than unattractive.

Please decide spontaneously. Don't think too long about your decision to make sure that you convey your original impression.

Sometimes you may not be completely sure about your agreement with a particular attribute or you may find that the attribute does not apply completely to the particular product. Nevertheless, please tick a circle in every line.

It is your personal opinion that counts. Please remember: there is no wrong or right answer!

Please assess the product now by ticking one circle per line.

		1	2	3	4	5	6	7	
1.	obstructive	○	○	○	○	○	○	○	supportive
2.	complicated	○	○	○	○	○	○	○	easy
3.	inefficient	○	○	○	○	○	○	○	efficient
4.	confusing	○	○	○	○	○	○	○	clear
5.	boring	○	○	○	○	○	○	○	exciting

6.	not interesting	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	interesting
7.	conventional	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	inventive
8.	usual	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	leading edge






Acceptance and Trust

By selecting the appropriate number, please read each statement and indicate your degree of agreement. There are no right or wrong answers.

	Strongly disagree	Disagree	Nor disagree or agree	Agree	Strongly agree
Effort expectancy					
1. Learning how to use [technology] is easy for me.	1	2	3	4	5
2. My interaction with [technology] is clear and understandable.	1	2	3	4	5
3. I find [technology] easy to use.	1	2	3	4	5
4. It is easy for me to become skillful at using [technology].	1	2	3	4	5
Perceived trust					
5. The system works reliably.	1	2	3	4	5
6. I am confident about the system's capabilities.	1	2	3	4	5
7. The system is capable of interpreting situations correctly.	1	2	3	4	5
8. I trust the system.	1	2	3	4	5
9. I can rely on the system.	1	2	3	4	5
Behavioral intention					
10. I intend to continue using [technology] in the future.	1	2	3	4	5
11. I will always try to use [technology] in my daily life.	1	2	3	4	5
12. I plan to continue to use [technology] frequently.	1	2	3	4	5






System Usability Scale (SUS) - age 7-8

By selecting the appropriate number, please read each statement and indicate your degree of agreement. There are no right or wrong answers.

Statement	1	2	3	4	5
					
	I Strongly disagree	I Disagree	I Do not Agree OR Disagree	I Agree	I Strongly agree
1. I would like to play [app] a lot more	1	2	3	4	5
2. [app] was hard to play	1	2	3	4	5
3. I thought [app] was easy to use	1	2	3	4	5
4. I would need help to play [app] more	1	2	3	4	5
5. I knew what to do next when I played [app]	1	2	3	4	5
6. Some things in [app] made no sense	1	2	3	4	5
7. [app] would be easy for my friends to learn	1	2	3	4	5
8. To play [app] I had to do some weird things	1	2	3	4	5
9. I was proud of how I played [app]	1	2	3	4	5
10. There was a lot to learn to play [app name]	1	2	3	4	5
11. Playing [app name] was fun	1	2	3	4	5
12. If we had more time, I would keep playing [app]	1	2	3	4	5
13. I plan on telling my friends about [app]	1	2	3	4	5

System Usability Scale (SUS) - age 9-11






By selecting the appropriate number, please read each statement and indicate your degree of agreement. There are no right or wrong answers.

Statement	1	2	3	4	5
					
	I Strongly disagree	I Disagree	I Do not Agree OR Disagree	I Agree	I Strongly agree
1. If I had this [app] on my iPad, I think that I would like to play it a lot	1	2	3	4	5
2. I was confused many times when I was playing [app]	1	2	3	4	5
3. I thought [app] was easy to use	1	2	3	4	5
4. I would need help from an adult to continue to play [app]	1	2	3	4	5
5. I always felt like I knew what to do next when I played [app]	1	2	3	4	5
6. Some of the things I had to do when playing [app] did not make sense	1	2	3	4	5
7. I think most of my friends could learn to play [app] very quickly	1	2	3	4	5
8. Some of the things I had to do to play [app] were kind of weird	1	2	3	4	5
9. I was confident when I was playing [app]	1	2	3	4	5
10. I had to learn a lot of things before playing [app] well	1	2	3	4	5
11. I really enjoyed playing [app]	1	2	3	4	5
12. If we had more time, I would keep playing [app]	1	2	3	4	5

13. I plan on telling my friends about [app]	1	2	3	4	5
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System Usability Scale (SUS) - age 12-18

By selecting the appropriate number, please read each statement and indicate your degree of agreement. There are no right or wrong answers.

Statement	1	2	3	4	5
					
	I Strongly disagree	I Disagree	I Do not Agree OR Disagree	I Agree	I Strongly agree
1. I think that I would like to use this	1	2	3	4	5
2. I found the system unnecessarily complex	1	2	3	4	5
3. I thought the system was easy to use	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use this system	1	2	3	4	5
5. I found the various functions in this system were well integrated	1	2	3	4	5
6. I thought there was too much inconsistency in the system	1	2	3	4	5
7. I would imagine that most people would learn to use this system very quickly	1	2	3	4	5
8. I felt the system was cumbersome to use	1	2	3	4	5
9. I felt very confident using the system	1	2	3	4	5
10. I needed to learn a lot of things before I could get	1	2	3	4	5

going with this system					
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Dietary habits and physical activity (daily questions)

Questions for daily measurements (Source: provided by UKCM)

The questions have been adapted in a way to be used as diary questions.

Nutritional issues

(To be completed by parents/guardians, mark with a number, description or 'X' for the appropriate answer)

1. How many meals did the child eat today?

1	2	3	4	5	more
---	---	---	---	---	------

2. Which meals did the child eat (choose all that apply)?: breakfast, lunch, dinner, snack, other

3. Which of these was the heartiest meal (choose one)? breakfast, lunch, dinner, snack

4. Did the child eat breakfast today?

1 yes	2 no
-------	------

5. Where did the child eat today? (choose all that apply)

1 only at home	2 at school	3 additionally with grandparents	4 outside
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6. Did the family have a meal together today?

1 yes	2 no
-------	------

7. How many eggs did the child eat today?

1	2	3	4	5	6	7	8	9	more
---	---	---	---	---	---	---	---	---	------

8. Was meat on the menu today?

1 yes	2 no
-------	------

9. How many teaspoons of sugar did (s)he drink in a cup of tea today?

1	2	3	4 more	5 Didn't have tea
---	---	---	--------	-------------------

10. Has (s)he eaten sweets today? Yes no

1 yes	2 no
-------	------

11. How many glasses of milk (2 dcl) did (s)he drink today?

1	2	3	4	5	6	7	8	9	more
---	---	---	---	---	---	---	---	---	------

12. Was there fruit on your child's menu today?

1 yes	2 no
-------	------

13. Did the child eat vegetables today?

1 yes	2 no
-------	------

14. How much bread did (s)he eat today?

1 up to 200g	2 up to 0.5 kg	3 more than 0.5 kg	4 does not consume bread
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15. What kind of bread did your child eat (choose all that apply)?

White bread	Rye bread	Bread with seeds	Sourdough	Corn bread	Spelt bread	Wholegrain	Other
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16. How much fluid did (s)he drink today?

up to 0.5 L	up to 1 L	up to 1.5 L	up to 2 L	more
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17. What kind of liquid did (s)he consume today?

1 water	2 fruit juice	3 iced tea	4 Fanta/Coca-cola	5 other
---------	---------------	------------	-------------------	---------

18. Did (s)he buy extra food himself/herself today?

1 yes	2 no
-------	------

19. Today, did (s)he eat food while:

a. watching TV?	1 yes	2 no	3 I don't know
b. listening to music?	1 yes	2 no	3 I don't know
c. learning?	1 yes	2 no	3 I don't know
d. reading the book?	1 yes	2 no	3 I don't know
e. I work on the computer?	1 yes	2 no	3 I don't know

20. Did (s)he go to bed today with a full stomach?

1 yes	2 no
-------	------

21. How do you rate the child's today's meals?

1 Small	2 medium	3 large
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22. How much time did it take for each meal today? _____ min

23. Who mainly prepared the child's food?

parents/caregivers	siblings	himself/herself	school staff	grandparents	Bought elsewhere	other
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Physical activities

(To be completed by parents or the child's companion)

1. Did the child exercise today at school?

1 yes	2 no
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2. Did (s)he do extra sports today?

1 yes	2 no
-------	------

3. His/her main activity outside school today (free time):

Free play – physically active	Free play - inactive	Walking	TV, video games or computer	Structured sport/practice	Other
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IF other, write here:

4. How many hours did (s)he sit at home today (excluding school, consider studying, reading, TV, computer...)?

1	2	3	4	5	6	7	8	9	more
---	---	---	---	---	---	---	---	---	------

5. How many hours did (s)he sleep the previous day? _____ hours

6. Did (s)he drive to school today (by bus or by car)?

1 yes	2 no
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7. Did (s)he walk today to school?

1 yes	2 no
-------	------

8. Distance of school from home: _____ km

Patients and caregivers cost questionnaire

Questionnaire for the estimation of direct and indirect costs incurred for healthcare services provided by providers outside the referring hospital

Role of the interviewee:

- Caregiver
- Patient

1. **Did the subject have any hospitalization related to obesity during the study period (from baseline to follow-up)?**

- Yes
- No

If yes, please fill the table below.

Hospitalization	Reason for the hospitalization (and DRG code, if available)	Duration (days)	Payment (out of pocket / private insurance or
-----------------	---	-----------------	---

			NHS / public insurance)
1			
2			
3			
4			
5			
6			
7			
8			

2. Did the subject receive any outpatient service (including rehabilitation) related to her/his obesity status during the study period (from baseline to follow-up)?

- Yes
- No

If yes, please fill the table below.

Outpatient activity (eg. blood test; cholesterol; rehabilitation – type; ultrasound; specialist visit; nutritional visit...)	Number of services provided	Payment (out of pocket / private insurance or NHS / public insurance)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

3. Did the subject receive any drug related to her/his obesity status during the study period (from baseline to follow-up)?

- Yes
- No

If yes, please fill the table below.

Drug	Posology	Payment (out of pocket / private insurance or NHS / public insurance)
1		
2		
3		
4		
5		

4. Did the subject receive any emergency visit related to her/his obesity status during the study period (from baseline to follow-up)?

- Yes
- No

If yes, please fill the table below.

Emergency visit	Reason	Payment (out of pocket / private insurance or NHS / public insurance)
1		
2		
3		
4		
5		

5. Did the subject receive any general practitioner visit related to her/his obesity status during the study period (from baseline to follow-up)?

- Yes
- No

If yes, how many visits were performed during the study period (from baseline to follow-up)?

6. Did any of the caregivers lost any working day due to the obesity condition of the subject during the study period (from baseline to follow-up)?

- Yes
- No

If yes, how many days of work were lost during the study period (from baseline to follow-up)?
