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HYBRIDA

D2.2: A traditional health technology assessment of organoids and organs-on-chips

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Project title: Embedding a comprehensive ethical dimension to organoid-based research and related technologies

Project acronym: HYBRIDA

Coordination and Support Action
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Project full title

"Embedding a comprehensive ethical dimension to organoid-based research and related technologies"

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HYBRIDA

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D2.2: A traditional health technology assessment of organoids and organs-on-chips

Deliverable factsheet

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1.	Coordinator of WP2	University of Oslo	UIO	Norway
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Executive summary

In the HYBRIDA project, one objective is to explore epistemological uncertainty in organoid research and to assess the impact of organoid-related technologies when translated from research to clinical use.

As a part of work package 2, we performed a traditional health technology assessment (HTA) of organoids. We mapped and assessed evidence in the scientific literature for their efficacy, effectiveness, safety and cost-effectiveness in clinical applications. Furthermore, we tried to identify deficiencies in evidence generation with this method of assessment. Ethical, legal and social aspects of health technologies were investigated in other parts of HYBRIDA.

Here, we provide the first HTA of organoids and organoid-based technologies. We searched the scientific literature for randomized, controlled trials (RCT) that have applied and investigated organoids. We included any registered, planned, ongoing, discontinued or completed trials that reported clinically relevant outcomes based on a set of predefined selection criteria.

We found no RCT that reported clinical effectiveness or other relevant outcomes of organoids. We found three registered RCT that plan to investigate organoids and measure clinical outcomes in the future. We were unable to conduct an assessment of the cost-effectiveness of organoids because we currently have no RCTs measuring their putative clinical efficacy.

High expectations for the clinical application of organoids are expressed in the review literature, but outcomes from RCTs demonstrating any clinical uses have not yet been reported. Ongoing studies indicate that such clinical outcomes may be expected within the next ten years. Other types of studies may provide evidence of the usefulness of organoids for the treatment of patients. We will assess this research in an amended HTA (see project deliverable 2.3).

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Part 1:

INTRODUCTION

1 The HYBRIDA project

Organoid research today comes with ambitious promises of revolutionizing biomedical research in the future and our view of the human organism and life itself. As this train of thought figuratively is leaving the station, it is important that ethics not only follows or lags behind, but is present on the train, shaping the journey as it is chartered.

The overall objective of project HYBRIDA is to develop a comprehensive regulatory framework for organoids and related technologies, such as organs-on-chips (OoC) platforms.

1.1 Organoids, organs-on-chips and their promises

An **organoid** is a self-organized or self-assembled cluster of cells, usually derived from stem cells or cancer cells from a patient and generated *in vitro*, i.e., outside the living organism, e.g., in a dish or test tube by virtue of tissue culturing methods.

Stem cells may be pluripotent, e.g., embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC), or derived from adult tissue, e.g., adult stem cells (ASC), cancer cells and cancer stem cells (CSC). By using organ-specific cell types, such entities might serve as three-dimensional (3D) culture models, mimicking the structural and functional properties of different organs, both human and non-human, such as the brain, heart, intestine, kidney, pancreas, liver, inner ear, retina or skin. Organoids of different origin, i.e., tissue types or organs, may be combined *in vitro* into what have been called “assembloids”.

An **organ-on-a-chip** (OoC) is a form of physiological system with the purpose of mimicking the functions and possible malfunctions of an organ. OoC are not the result of self-organization or self-assembly of cells, but carefully engineered and controlled microscopical systems (chips). To produce OoC, cells are cultured in the dynamic

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microenvironments of microfabricated biochips, i.e., high-tech devices or lattices with perfused chambers that may emulate blood flow and other physical or chemical properties that resemble live cells and functions in living organisms. OOC may be combined into systems, representing two, three or several organs that interact. **Organoids-on-a-chip** is a term sometimes used when whole organoids, not individual cells, are grown on and controlled by such chips. There are scientific and technological ambitions to build "bodies-on-chips" or "humans-on-chips" (1, 2).

Organoids and OoC systems are often contrasted to and seen as an extension of simpler *in vitro* and *in silico* models of human disease and physiology, including genomic sequences and sophisticated computer models. Moreover, they often stand in contrast to *in vivo* experimental animal models.

Because science and human knowledge rely on models, and because there are ethical limitations to experimenting with humans, a scientific frontier is presently exploring the best possible and most representative *in vitro* models of health and disease. Organoids, OoC and other micro-physiological systems have the potential of providing improvements to existing biomedical models and may result in a more complete scientific understanding of human physiology, and ultimately, patient treatment. The aforementioned models are increasingly used in basic and preclinical research as well as drug discovery, development and testing.

Because three-dimensional and chip-based artificial organoids and organ systems are derived from human individuals, they could, in principle, represent a patient's unique physiology and disease. Therefore, these systems may be used to better understand, diagnose and treat a person's particular disease. By testing drugs or other treatments to predict the putative effect for a particular person, organoids and OoC are envisioned by some to lead to better personalized and precision medicine (1, 3).

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1.2 Project outline

The main idea behind the HYBRIDA project is that organoids and related technologies challenge a longstanding dualism: since Roman law, all entities have been categorized and regulated either as persons (subjects) or things (objects). Organoids may be viewed as a disruptive innovation that challenges this conceptual, epistemological[1] and regulatory dualism by introducing three corresponding forms of uncertainty (see also Figure 1):

First, ***conceptual (ontological[2]) uncertainty***: How should one conceive of living entities that cannot be categorized as either persons or things? What *are* they?

Second, ***epistemological and methodological uncertainty***: How can we gain knowledge about something that is neither a person nor a thing? This is particularly pertinent where organoids and OoC are intended for personalized medicine. Here, they may serve as representations of or "stand-ins" for the person they were derived from. Organoids may be construed as "avatars" of the person, so similar in physiology and function that they may provide clinically critical knowledge (1).

In some instances of organoid and OoC use, "traditional" methods of evidence-based medicine may provide sufficient evidence. In precision medicine, however, one person is unlike other research subjects, which hampers experimental comparison by traditional randomized controlled trials (RCTs) and other study types that need to be sufficiently powered to allow statistical interpretation.

This raises the question how we can hope to gain knowledge and make predictions based on such models. What uncertainties do we face in this branch of medicine? How do we address uncertainties and assess risks if we cannot apply common statistical methods?

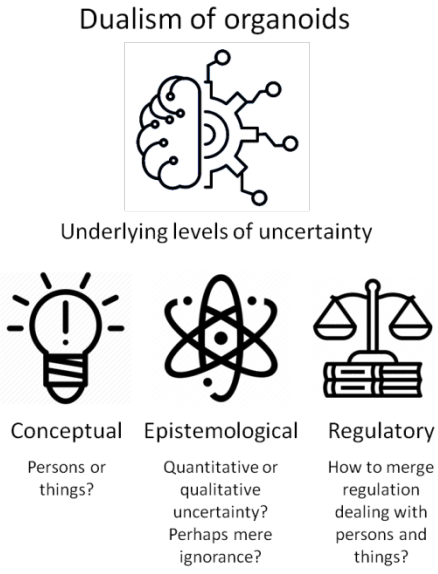

***Figure 1**. Levels of uncertainty stemming from the dual nature of organoids*

Things have the attribute that they may be standardized and manufactured as true replicas. Organoids do not have this attribute. As precision medicine and new technologies emerge, evidence-based medicine is challenged to find a new footing.

[1] **Epistemology** is the branch of philosophy concerned with the nature, origin and scope of knowledge and the rationality of belief.

[2] **Ontology** is the branch of philosophy that studies concepts such as existence, becoming and reality, and seeks to answer how entities are grouped under basic categories and which entities exist on a fundamental level.

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Third, ***regulatory uncertainty*** emerges because parts of regulatory frameworks concerning the rights and duties of persons have been merged with elements of regulation dealing with the stewardship of objects or things. These forms of uncertainty are of particular importance to ethical and legislative interpretations and applications of organoids.

HYBRIDA addresses these three kinds of uncertainty. We aim to communicate the potential pitfalls of organoid research to help develop a sound regulatory framework.

Several work packages (WP), each delivering its own products and reports, together comprise the project of embedding organoid-based research and related technologies in comprehensive ethics. Figure 2 outlines project HYBRIDA and its WPs.

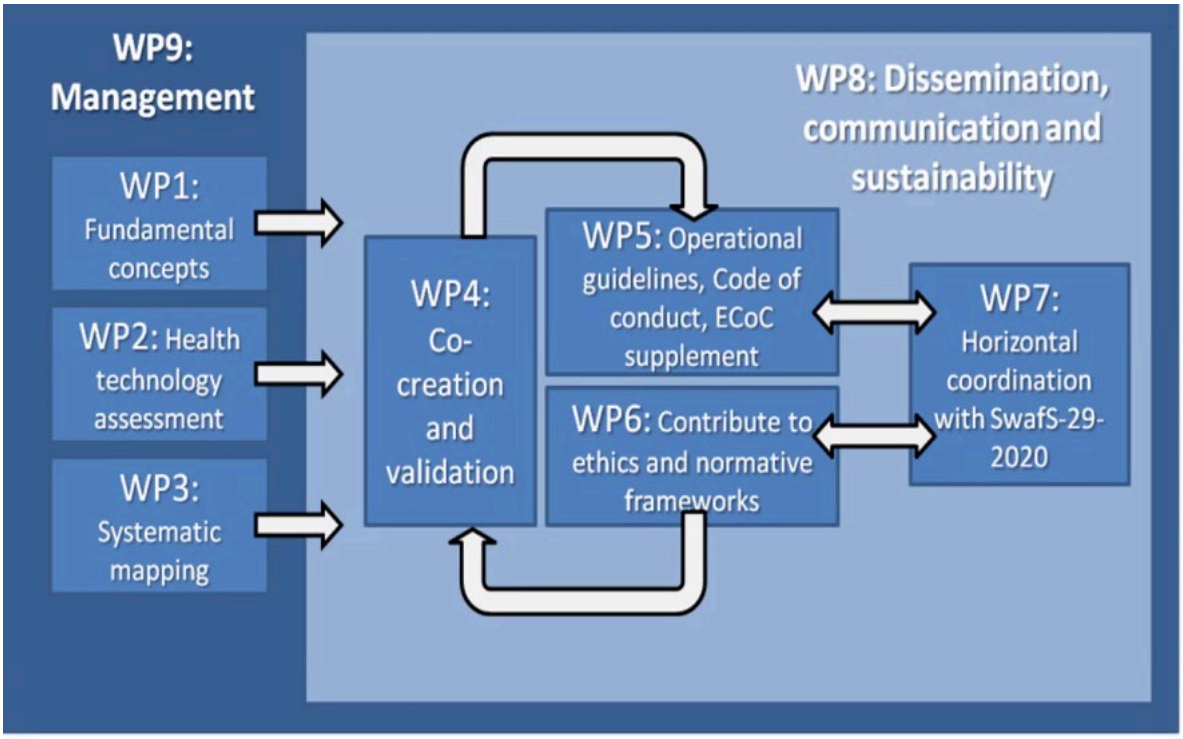

Figure 2. *Program evaluation and review technique (PERT) chart of the HYBRIDA project workflow depicting its work packages (WP). Arrows indicate the flow of information between different work packages (confer also Figure 4 in the HYBRIDA proposal).*

1.3 Work package 2

WP2 performed a mapping of the organoid field that will inform WP4 and be used by WP5 and 6 as their factual base (see Figure 2 above). This map will identify current avenues of organoid research and provide an overview of important features of this research, e.g., origins and types of organoids and their research purposes. A separate mapping has tried to

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capture current developments in organoid research and their translation from the laboratory to clinical or industrial use.

Two aims of WP2 are to apply both a "traditional" and an "amended" method of health technology assessment (HTA) of organoids by addressing epistemological and methodological uncertainties, i.e., questions of evidence for and uncertainty of the utility of these technologies in the setting of personalized medicine.

WP2 had the following tasks and corresponding deliverables (in the form of reports):

- T2.1: Mapping of the organoid field, including types of organoids, origins of cells, purpose of research, planned and potential translations (Report D2.1).
- T2.2: A HTA looking primarily at evidence from randomized controlled trials for the efficacy, effectiveness and cost-effectiveness of organoids applied in clinical research (this report).
- T2.3: The development of an amended HTA to examine other evidence and epistemological uncertainty pertaining to organoid and OoC use in personalized medicine (Report D2.3).
- T2.4: The application of the method applied in T2.3 to complement T2.2 and produce a comprehensive, amended HTA (Report D2.4).

In this part of WP2, we performed what we designate a "traditional HTA" of organoids which should serve as a benchmark. We expect, as organoids pose challenges to traditional statistical assessments of safety, effectiveness, and efficiency (cf. Project outline above), that new modes of assessment need to be developed and implemented.

The results from WP1 and the results from the current report will be used as points of departure for developing an "amended HTA" methodology. Project deliverables D2.2, providing a traditional HTA as described here, will inform project deliverable D2.3. Together, these deliverables will lay the theoretical foundation for an amended HTA, to be conducted in project deliverable D2.4. The amended HTA will be added to our current results to provide a more comprehensive map of organoids and OoC technologies, focusing on epistemological issues and their links to conceptual and ethical problems.

2 Task specification and scope

In WP2, we try to identify and address epistemological uncertainties of organoid research and their possible ethical and societal implications. In task 2.2 of WP2, we performed a traditional HTA, i.e., we mapped and assessed evidence on the efficacy, effectiveness, safety, and cost-effectiveness of organoids and OoC as emerging health technologies as they may be used in clinical applications. Emergent technologies according to Brey 2012 (4), are "*[…] at an early stage of development and have not yielded many*

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applications and societal consequences. They are still largely, or fully, at the research and development stage, meaning that they are still at the stage of research into basic techniques, or at an early stage of development which at most has resulted in lab prototypes and experimental applications but little or no serious products that are being used by ordinary users."

Efficacy and **effectiveness** both refer to how well a technology works, i.e., whether it accomplishes its intended purpose, usually based on changes in one or more specified health outcomes or "endpoints". A technology that works well under carefully managed conditions (efficacy) does not always work the same way under more heterogeneous or less controlled conditions (effectiveness). Accordingly, in the context of a HTA, efficacy *refers* to the benefit of using a technology for a particular problem under ideal conditions, e.g., within the protocol of a carefully managed RCT, involving patients meeting narrowly defined criteria, or conducted at a "center of excellence." *Effectiveness* refers to the benefit of using a technology for a particular problem under general or routine conditions, e.g., by a physician in a community hospital for a variety of types of patients (5). Whereas *efficacy* answers the question "Can it work?" (under ideal conditions), effectiveness answers the question "Does it work?" (under real-world conditions). **Safety** is a judgment of the acceptability of risk (the probability of an outcome and its severity) when using a technology in a given situation, e.g., for a patient with a particular health problem, by a clinician with certain training, or in a specified treatment setting (5).

Clinical applications of organoids include their use to predict treatment outcomes in personalized medicine and their transplantation in regenerative medicine. We did not investigate organoids as research models *per se* or as tools for applications other than patient treatment, e.g., for drug testing and screening. We included published RCTs that have reported such outcomes as well as planned and ongoing clinical trials that may add such evidence in the future (see 4 Methodology on page 13ff).

Furthermore, we tried to identify deficiencies with this method of assessment. We did not investigate social, ethical and legal aspects of organoid research as these were evaluated in other parts of HYBRIDA (WP1, report D2.4 of WP2, and WP3).

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Part 2:

METHOD

3 Health technology assessment

According to the National Institutes of Health, "Technology is the practical application of knowledge. Health technology is the practical application of knowledge to improve or maintain individual and population health." (5)

The purpose of our "traditional" HTA was to assess the impact of technology on society and human life. An HTA can briefly be defined as "*the systematic evaluation of properties, effects, or other impacts of health technology*" (5), with the main purpose of informing policymaking and decision-making in a wide sense. More specifically, it may be defined as a "*multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system*" (6, 7). Health technologies have been assessed even before the term technology assessment (TA) appeared in the mid-1960s.

Historically, it may be said that there are two strands of HTA research that are quite different in origin and distinct (although there are attempts to integrate them). One strand has its roots in clinical epidemiology and economics, with a strong focus on quantitative methods, especially RCTs and systematic reviews and meta-analyses. This is closely linked to evidence-based medicine, which is predominantly used in HTA and ranks the strength of results from scientific research hierarchically, where systematic reviews and RCTs are deemed to provide the highest quality of clinical evidence (8).

The second strand has its roots in science and technology studies (STS) and applied ethics. It seeks to incorporate social issues and ethics and to use more qualitative methods and methods from the humanities (9). The ideas of vision assessment, i.e. assessing expectations, represent the latter strand.

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Practitioners of HTA are traditionally committed to comprehensiveness as HTA sprang out of an awareness that a health technology can have profound, unintended and unforeseen consequences, including individual benefits and harms as well as cultural, social, ethical, legal and political implications (5, 7). High costs associated with the introduction and proliferation of a new health technology are also a concern. Therefore, "*despite this original impetus for HTA to perform this comprehensive study of implications of health technology, its focus has been often narrowed to issues of affordability*" (7). At the same time, in keeping with distinction between fact and value, questions of safety, clinical effectiveness and cost-effectiveness are often addressed using quantitative, statistical methods in randomized, controlled trials. Ethical, legal and social issues are often considered separately from safety, clinical effectiveness and cost-effectiveness (7).

In this report, by "traditional" HTA we mean an analysis that reviews and assesses quantitative research evidence, particularly RCTs, to answer questions of safety, clinical effectiveness and cost-effectiveness.

4 Methodology

We hypothesized that organoids or OoC may have been used to treat patients and that scientific evidence from clinical trials may exist. We systematically searched for published research that applied and investigated any organoids or OoC in RCTs and reported clinically relevant outcomes.

4.1 Literature searches

The purpose of our literature searches was to map clinically relevant outcome measures in the organoid literature. A mapping of clinically relevant outcome targets will provide an important overview of the values at stake (and can also be used to identify types of uncertainty). They will also be relevant for the final (amended) method evaluation.

We searched for reports of organoids or OoC derived from any organ or tissue and synonyms thereof. We limited our searches to systematic reviews, HTAs and RCTs as these study types meet the strictest requirements and provide the highest level of evidence for this traditional HTA.

We did not search for non-randomized controlled trials or trials without control groups. We did not search studies of experimental animal models. We did not search for other types of scientific literature, including editorials, interviews, letters, legal reports and congress abstracts.

The keywords and synonyms used in our search strategies are described in detail in the Appendix to this report; see pages 25ff below.

We searched the following databases on July 13, 2021:

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- MEDLINE (Ovid)
- Embase (Ovid)
- Cochrane Database of Systematic Reviews (Wiley)
- Epistemonikos
- Scopus (Elsevier)

We searched the following registers on July 13, 2021:

- Cochrane Central Register of Controlled Trials (Wiley)
- ClinicalTrials.gov

We stored all references that we retrieved in our literature searches in Endnote (10) and removed duplicate references. We then used Covidence (11) to sort and select references. The software automatically identified and excluded additional duplicate records (see Figure 3).

4.2 Selection of relevant studies

We defined criteria for study selection as shown in Table 1 below.

When selecting relevant studies, we included only registered, completed RCTs, as well as any planned, ongoing and discontinued clinical trials.

Two researchers read the titles and abstracts of each reference independently of one another and decided whether to include or exclude the study based on our predefined selection criteria presented in Table 1 above. Conflicting decisions were resolved by a third researcher who assessed the title and abstract and made a final decision on study inclusion or exclusion.

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Table 1. Inclusion and exclusion criteria for study selection

	Criteria for inclusion	Criteria for exclusion
Population	Human participants in clinical trials regardless of age, gender, medical condition or other biological or socioeconomic parameters	
Intervention	Any type of organoid except bone or cartilage tissue	Organoids derived from bone or cartilage tissue as these organoids are not usually derived from stem cells
Comparison	Any comparison such as placebo or any other control	Studies without a control group
Outcome	Any clinically relevant outcome, e.g., efficacy, effectiveness, or clinical benefit	Studies that reported only safety, side effects or adverse events, cost-benefit calculations or economic models
Study design	Planned, ongoing, discontinued and completed randomized controlled trials	Non-randomized trials and studies that did not report results from human patients
Publication type	Original research articles as well as planned and ongoing studies published in scientific journals and clinical trial registers	
Language		Articles published in languages we were unable to translate

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Part 3:

RESULTS

5 Clinical utility of organoids

5.1 Randomized, controlled trials reporting clinical outcomes

Figure 3 below depicts a flow chart of the literature searches and the results from screening the retrieved literature.

We found no published RCT that met our criteria (see Table 1 above) and that reported measured clinical outcomes of organoid research. However, such studies may be published in the future as there are RCTs that are currently ongoing or registered, and that plan to report clinical outcomes.

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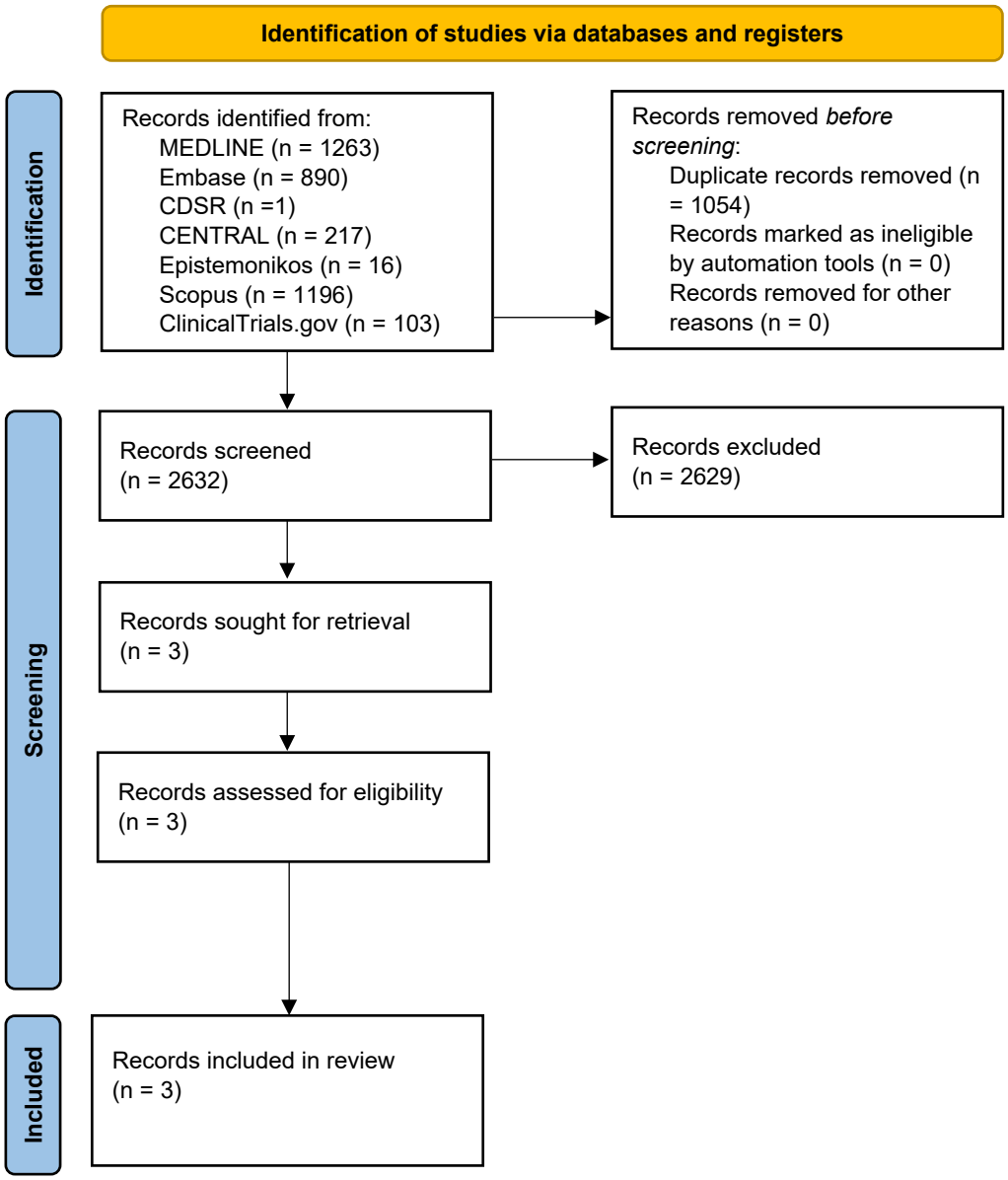

***Figure 3**. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (15)*

5.2 Planned and ongoing randomized, controlled trials

We found three registered clinical trials that plan to test the usefulness of organoids for selection of therapies in patients with rectal or pancreatic cancer (12-14); see

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Table **2**.

Table 2. Ongoing RCTs planned to report clinical outcomes from organoids

Title	Principal Investigator	Type of organoid	Design	Status	Planned completion	Patients needed
Systemic Neoadjuvant and Adjuvant Control by Precision Medicine in Rectal Cancer (SYNCOPE) (12)	Toni T. Seppälä, Helsinki, Finland	Rectal cancer	Randomized Parallel Controlled Open Label	Not yet recruiting	December 2031	93
Organoid-Guided Chemotherapy for Advanced Pancreatic Cancer (13)	Gang Jin, Shanghai, China	Pancreatic cancer	Randomized Parallel Controlled Open Label	Recruiting	May 2025	100
Pancreatic Adenocarcinoma Signature Stratification for Treatment (PASS-01) (14)	Elizabeth Jaffee, Baltimore, USA and Jennifer J Knox, Toronto, Canada	Pancreatic cancer	Randomized Parallel Controlled Open Label	Recruiting	September 2023	150

The investigators plan to compare conventional treatment strategies with treatment guided by the results *in vitro* drug tests of patient-derived organoids in a randomized fashion. These studies aim to enroll roughly 100 to 150 patients and measure several clinical and patient-relevant outcomes, including, among other parameters, tumor progression-free and overall survival, response rates to therapy, control of disease, recurrence of tumor and metastasis, as well as adverse events and postoperative complications. The investigators expect these results within two to ten years from now.

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Part 4:

DISCUSSION

6 Current state of organoid research

Despite a longstanding history of organoid research and considerable funding (cf. report D2.1), this traditional HTA approach did not identify any clinically relevant outcomes from using organoids or OoC in RCTs. Some ongoing trials indicate that clinical results from using organoids may be available in the near future. Nevertheless, there is currently a gap between the expectations expressed by researchers in the review literature concerning the clinical applications of organoids, OoC and organoid-based technologies and the current state of this research. There may be reasons that support such expectations, such as results from preclinical testing and modelling based on experimental animal research as well as observational studies of human subjects. Do factors that support the expectations of clinical application and benefits from organoids or OoC serve as evidence of clinical efficacy in the absence of RCTs, systematic reviews, and HTAs?

All reported results we were able to find are from studies at an experimental or preclinical stage (16-25) supporting our finding that no RCTs are completed and published at this point in time. Current assessments will therefore have to rely on experimental and preclinical studies and analogical and abductive inferences from these (26).

Published reviews of organoid research covered (**a**) their use for *in vitro* modelling of testicular architecture, physiology and functionality (24); (**b**) modeling of diseases and transplantation in animals (20); (**c**) modeling of disease pathology (16); (**d**) the use of OoC as physiological and etiological models, for toxicity tests, and screening of pharmacological agents in order to select type and dosage of drug treatments (19); (**e**) the study of organ morphology, histology and physiology and tissue reconstruction (23); and (**f**) extracellular vesicles for cancer treatment, cardiac repair and stem cell studies (18).

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6.1 New modes of knowledge production and evidence assessment

This traditional HTA provides no evidence of clinically relevant outcomes from organoid research. Importantly, this does not mean that organoids or OoC are not clinically relevant. It only means that there is currently not sufficient evidence from RCTs and that such results are not expected to be found in HTAs in the near future.

There may be several reasons why no relevant reports or results currently exist. Clinical trials require a certain number of patients to be feasible, and they are often time consuming and resource demanding. Moreover, both personalized medicine (or precision medicine) as well as the currently ongoing pandemic has increased the urge for other criteria for evidence-production than traditional HTA (e.g., HTA+) (27).

If other types of study design could provide robust evidence of clinically relevant outcomes from organoids or OoC, we need other modes of evidence assessment than a traditional HTA. We have attempted to address this point in our amended HTA, see D2.3.

6.2 Cost-effectiveness, ethical, social, and legal aspects of organoid research

In this body of work, we found no evidence from RCTs on the clinical effectiveness of organoids or OoC. Therefore, it was impossible for us to conduct a thorough assessment of the clinical efficiency or cost-effectiveness of organoids. While there are some initial studies on cost-effectiveness of organoids for specific fields (28), most studies only point to their potential and do not provide scientific evidence on cost-effectiveness.

There are a number of approaches to address the social (29) and ethical (30-35) aspects of a given technology in HTA. These aspects were not investigated in this report, but in other parts of HYBRIDA (see WP3).

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7 Conclusion

We provide the first systematic review of RCTs using organoids or OoC. We found no clinical outcomes from RCTs. We found three registered RCTs that involve organoids. Ongoing studies indicate that clinical outcomes may be demonstrated in the future. Our review of literature reviews revealed that organoid research hitherto has for the most part investigated technical aspects and preclinical models.

We think it is crucial to assess new technologies that emerge from organoid research at an early stage. This HTA may have come prematurely, but it points out the current lack of clinical applications of organoids. This result is relevant for the following amended HTA and for similar assessments of organoids as possible health technologies in the future.

8 Acknowledgements

We are most thankful to Hilde Strømme and Toril Marie Hestnes at the University of Oslo Library for designing and performing the literature searches. We want to thank Henrik Vogt at the University of Oslo for letting us use some of his intellectual property in this report, specifically in Part 1 Introduction, which was written for report D2.3 of this work package.

Disclaimer

A more extensive systematic review has been accepted for publication in the journal Cells, Tissues & Organs on September 2, 2022. The article is titled Organoids in the clinic: a systematic review of outcomes by Bjørn Hofmann (corresponding author), Severin Zinöcker, Søren Holm, Jonathan Lewis and Panagiotis Kavouras (co-authors), and this report is partly based on this systematic review.

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10 Appendix

Hilde Strømme, academic librarian at the Library of Medicine and Science, University of Oslo, on July 13, 2021, searched the following databases and registers:

Database	Number of retrieved references
MEDLINE (Ovid)	1263
Embase (Ovid)	890
Cochrane Database of Systematic Reviews (Wiley)	1
Cochrane Central Register of Controlled Trials (Wiley)	217
Epistemonikos	16
Scopus (Elsevier)	1196
ClinicalTrials.gov	103
Number of references before deduplication:	**3686**
Number of references after deduplication:	**2643**

Ovid MEDLINE(R) ALL <1946 to July 12, 2021>

#	Searches	Results
1	Organoids/	10581
2	(organoid* or enteroid* or colonoid* or ((organ* or tissue* or (multi adj organ*) or human or body or disease* or tumor* or tumour* or cancer* or neoplasm* or liver* or stomach* or gut or intestine* or pancreas or heart* or vessel* or artery or arteries or vein* or lung* or airway* or kidney* or brain* or encephalon* or nerve* or ovary or ovaries or placenta* or prostate* or spleen* or (bone adj marrow) or (lymph adj node*) or muscle* or bone* or eye* or lens or lenses or retina or skin or derma or cutis) adj3 chip*)).tw,kf.	12867
3	1 or 2	20684
4	randomized controlled trial.pt.	537443
5	controlled clinical trial.pt.	94291
6	randomized.ab.	526716
7	placebo.ab.	219711
8	drug therapy.fs.	2347774
9	randomly.ab.	361446
10	trial.ab.	559671
11	groups.ab.	2219427
12	or/4-11	5059649
13	exp animals/ not humans.sh.	4860245
14	12 not 13	4399447
15	3 and 14	1179
16	(meta-analysis or systematic review).pt.	229979
17	meta-analysis/ or systematic review/ or exp meta-analysis as topic/ or Systematic Reviews as Topic/ or exp Technology Assessment, Biomedical/	262885
18	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	232994
19	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	12469

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20	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	31044
21	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	31402
22	(handsearch* or hand search*).ti,ab,kf,kw.	9916
23	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	29465
24	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	10295
25	(meta regression* or metaregression*).ti,ab,kf,kw.	10812
26	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	360552
27	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	260904
28	(cochrane or (health adj2 technology assessment) or evidence report).jw.	20244
29	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	14899
30	(outcomes research or relative effectiveness).ti,ab,kf,kw.	10065
31	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	2404
32	or/16-31	540039
33	3 and 32	99
34	15 or 33	1271
35	34 not (editorial or interview or letter or congress or legal case or meeting abstract).pt.	1263

Applied filters: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format (36); Adapted version of Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO (37);

Embase Classic + Embase <1947 to 2021 July 12>

#	Searches	Results
1	exp organoid/	7079
2	(organoid* or enteroid* or colonoid* or ((organ* or tissue* or (multi adj organ*) or human or body or disease* or tumor* or tumour* or cancer* or neoplasm* or liver* or stomach* or gut or intestine* or pancreas or heart* or vessel* or artery or arteries or vein* or lung* or airway* or kidney* or brain* or encephalon* or nerve* or ovary or ovaries or placenta* or prostate* or spleen* or (bone adj marrow) or (lymph adj node*) or muscle* or bone* or eye* or lens or lenses or retina or skin or derma or cutis) adj3 chip*)).tw,kw.	18996
3	1 or 2	19495
4	Randomized controlled trial/	668171
5	Controlled clinical trial/	463850
6	random*.ti,ab.	1693825
7	randomization/	91412
8	intermethod comparison/	272959
9	placebo.ti,ab.	331020
10	(compare or compared or comparison).ti.	572336
11	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2337447
12	(open adj label).ti,ab.	88590
13	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	251564
14	double blind procedure/	188082
15	parallel group*1.ti,ab.	27768
16	(crossover or cross over).ti,ab.	112925
17	((assign* or match or matched or allocation) adj5 (alternate or group*1 or intervention*1 or patient*1 or subject*1 or participant*1)).ti,ab.	360359

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18	(assigned or allocated).ti,ab.	424971
19	(controlled adj7 (study or design or trial)).ti,ab.	386470
20	(volunteer or volunteers).ti,ab.	264846
21	human experiment/	549545
22	trial.ti.	341303
23	or/4-22	5522256
24	(random* adj sampl* adj7 (cross section* or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	8742
25	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.)	274716
26	(((case adj control*) and random*) not randomi?ed controlled).ti,ab.	18667
27	(Systematic review not (trial or study)).ti.	179970
28	(nonrandom* not random*).ti,ab.	17187
29	Random field*.ti,ab.	2528
30	(random cluster adj3 sampl*).ti,ab.	1371
31	(review.ab. and review.pt.) not trial.ti.	904598
32	we searched.ab. and (review.ti. or review.pt.)	37407
33	update review.ab.	116
34	(databases adj4 searched).ab.	43855
35	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*1).ti. and animal experiment/	1113439
36	Animal experiment/ not (human experiment/ or human/)	2339927
37	or/24-36	3739834
38	23 not 37	4911915
39	3 and 38	1543
40	exp meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or biomedical technology assessment/	475197
41	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	289246
42	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kw.	14821
43	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	44116
44	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	38725
45	(handsearch* or hand search*).ti,ab,kw.	12076
46	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	39074
47	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw.	16788
48	(meta regression* or metaregression*).ti,ab,kw.	13460
49	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	570375
50	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	342916
51	(comparative adj3 (efficacy or effectiveness)).ti,ab,kw.	22130
52	(outcomes research or relative effectiveness).ti,ab,kw.	14866
53	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	4525
54	or/40-53	781035
55	3 and 54	162
56	39 or 55	1686
57	56 not (Conference abstract or Conference paper or Conference review or Editorial or Letter or Note or Short survey).pt.	890

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Applied filters: Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2018 revision); Ovid format (36); Adapted version of Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO (37);

Cochrane Database of Systematic Reviews: Cochrane Central Register of Controlled Trials

#	Searches	Results
#1	[mh ^"Organoids"]	2
#2	((organoid* OR enteroid* OR colonoid*) OR ((organ* OR tissue* OR (multi NEXT organ*) OR human OR body OR disease* OR tumor* OR tumour* OR cancer* OR neoplasm* OR liver* OR stomach* OR gut OR intestine* OR pancreas OR heart* OR vessel* OR artery OR arteries OR vein* OR lung* OR airway* OR kidney* OR brain* OR encephalon* OR nerve* OR ovary OR ovaries OR placenta* OR prostate* OR spleen* OR (bone NEXT marrow) OR (lymph NEXT node*) OR muscle* OR bone* OR eye* OR lens OR lenses OR retina OR skin OR derma OR cutis) NEAR/3 chip*)):ti,ab,kw	218
#3	#1 OR #2	218
#4	#3 in Cochrane Reviews, Cochrane Protocols	1
#5	#3 in Trials	217

Epistemonikos

(title:((title:((organoid* OR enteroid* OR colonoid* OR organ-on-a-chip OR tissue-on-a-chip OR human-on-a-chip OR body-on-a-chip OR disease-on-a-chip OR tumor-on-a-chip OR tumour-on-a-chip OR cancer-on-a-chip OR neoplasm-on-a-chip OR liver-on-a-chip OR stomach-on-a-chip OR gut-on-a-chip OR intestine-on-a-chip OR pancreas-on-a-chip OR heart-on-a-chip OR vessel-on-a-chip OR artery-on-a-chip OR vein-on-a-chip OR lung-on-a-chip OR airway-on-a-chip OR kidney-on-a-chip OR brain-on-a-chip OR nerve-on-a-chip OR ovary-on-a-chip OR placenta-on-a-chip OR prostate-on-a-chip OR spleen-on-a-chip OR muscle-on-a-chip OR bone-on-a-chip OR eye-on-a-chip OR lens-on-a-chip OR retina-on-a-chip OR skin-on-a-chip OR derma-on-a-chip OR cutis-on-a-chip)) OR abstract:((organoid* OR enteroid* OR colonoid* OR organ-on-a-chip OR tissue-on-a-chip OR human-on-a-chip OR body-on-a-chip OR disease-on-a-chip OR tumor-on-a-chip OR tumour-on-a-chip OR cancer-on-a-chip OR neoplasm-on-a-chip OR liver-on-a-chip OR stomach-on-a-chip OR gut-on-a-chip OR intestine-on-a-chip OR pancreas-on-a-chip OR heart-on-a-chip OR vessel-on-a-chip OR artery-on-a-chip OR vein-on-a-chip OR lung-on-a-chip OR airway-on-a-chip OR kidney-on-a-chip OR brain-on-a-chip OR nerve-on-a-chip OR ovary-on-a-chip OR placenta-on-a-chip OR prostate-on-a-chip OR spleen-on-a-chip OR muscle-on-a-chip OR bone-on-a-chip OR eye-on-a-chip OR lens-on-a-chip OR retina-on-a-chip OR skin-on-a-chip OR derma-on-a-chip OR cutis-on-a-chip)))) OR abstract:((title:((organoid* OR enteroid* OR colonoid* OR organ-on-a-chip OR tissue-on-a-chip OR human-on-a-chip OR body-on-a-chip OR disease-on-a-chip OR tumor-on-a-chip OR tumour-on-a-chip OR cancer-on-a-chip OR neoplasm-on-a-chip OR liver-on-a-chip OR stomach-on-a-chip OR gut-on-a-chip OR intestine-on-a-chip OR pancreas-on-a-chip OR heart-on-a-chip OR vessel-on-a-chip OR artery-on-a-chip OR vein-on-a-chip OR lung-on-a-chip OR airway-on-a-chip OR kidney-on-a-chip OR brain-on-a-chip OR nerve-on-a-chip OR ovary-on-a-chip OR placenta-on-a-chip OR prostate-on-a-chip OR spleen-on-a-chip OR muscle-on-a-chip OR bone-on-a-chip OR eye-on-a-chip OR lens-on-a-chip OR retina-on-a-chip OR skin-on-a-chip OR derma-on-a-chip OR cutis-on-a-chip)) OR abstract:((organoid* OR enteroid* OR colonoid* OR organ-on-a-chip OR tissue-on-a-chip OR human-on-a-chip OR body-on-a-chip OR disease-on-a-chip OR tumor-on-a-chip OR tumour-on-a-chip OR cancer-on-a-chip OR neoplasm-on-a-chip OR liver-on-a-chip OR stomach-on-a-chip OR gut-on-a-chip OR intestine-on-a-chip OR pancreas-on-a-chip OR heart-on-a-chip OR vessel-on-a-chip OR artery-on-a-chip OR vein-on-a-chip OR lung-on-a-chip OR airway-on-a-chip OR kidney-on-a-chip OR brain-on-a-chip OR nerve-on-a-chip OR ovary-on-a-chip OR placenta-on-a-chip OR prostate-on-a-chip OR spleen-on-a-chip OR muscle-on-a-chip OR bone-on-a-chip OR eye-on-a-chip OR lens-on-a-chip OR retina-on-a-chip OR skin-on-a-chip OR derma-on-a-chip OR cutis-on-a-chip)))))

Limited to Broad Synthesis (0 hits), Systematic Review (16 hits), Structured Summary (0 hits)

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Scopus

TITLE-ABS-KEY ((organoid* OR enteroid* OR colonoid*) OR ((organ* OR tissue* OR (multi W/0 organ*) OR human OR body OR disease* OR tumor* OR tumour* OR cancer* OR neoplasm* OR liver* OR stomach* OR gut OR intestine* OR pancreas OR heart* OR vessel* OR artery OR arteries OR vein* OR lung* OR airway* OR kidney* OR brain* OR encephalon* OR nerve* OR ovary OR ovaries OR placenta* OR prostate* OR spleen* OR (bone W/0 marrow) OR (lymph W/0 node*) OR muscle* OR bone* OR eye* OR lens OR lenses OR retina OR skin OR derma OR cutis) W/2 chip*)) AND ((TITLE-ABS-KEY ({Clinical-trial} OR {controlled-trial} OR randomi* OR randomly OR (random W/4 (allocat* OR distribut* OR assign*)) OR {placebo} OR (38) OR {groups} OR {subgroups}) OR TITLE (rct)) OR (TITLE-ABS-KEY (((systematic* W/2 (review* OR overview*)) OR (methodologic* W/2 (review* OR overview*))) OR ((quantitative W/2 (review* OR overview* OR synthes*)) OR (research W/2 (integrati* OR overview*))) OR ((integrative W/2 (review* OR overview*)) OR (collaborative W/2 (review* OR overview*)) OR (pool* W/2 analy*))))) AND (EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "le"))

Applied filters: Randomized Controlled Trials / Controlled Clinical Trials: A Cut and Paste Search Strategy for Scopus (39); Elements from Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO (37);

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