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1 Contents

2	Executive Summary.....	3
3	The Research Community and their Stakeholders.....	4
3.1	The Research Community.....	4
3.2	Stakeholders	5
4	Guidelines for the Research Community	7
4.1	Across disciplines within the Research Community	7
4.2	Towards the industry as end user	8
4.3	Towards the healthcare sector as end user and intermediary	8
4.4	Towards governmental end users and intermediary regulatory actors.....	9
4.5	Towards decision makers in government and investors.....	10
4.6	Towards the media as an intermediary.....	11
4.7	Towards the public at large	11
5	Conclusions	12
6	References	13

2 Executive Summary

This deliverable aims to provide a guideline for the research community working on Organ-on-Chip (OoC) topics for communication with stakeholders in their ecosystem. The ultimate goal is to identify and adequately respond to ethical implications in a timely and proper way. Relationships between researchers and stakeholders are driven by a multitude of forces which we will take as the starting point for further investigations.

Purpose: OoC technologies are not yet common or mainstream tools. They have great potential to mediate significant improvements and changes to processes and practices in drug toxicity and safety of cosmetics or chemicals, pharmaceutical drug development including improving drug efficacy, personalised therapies, and fundamental understanding of disease mechanisms. Collaborations primarily involve members of the research community. The impact, however, will be seen by patients, clinicians, regulatory agencies, governmental health departments and health insurance companies. Some of those may appear as rather distant stakeholders but their engagement is nevertheless necessary. Appropriate dialogue with the different players in the ecosystem on expectations, opportunities and risks is important to bring them on board and give OoC technologies a well-understood and supported place in a changing society. Being a novel technology, it is important that the research community itself actively engages in such dialogue. This deliverable aims at providing a guideline for the research community to achieve this.

Methodology: An overview of ethical implications in the use of OoC technologies has been prepared in Deliverable D5.1, largely based on literature and media studies. The SWOT analysis revealed gaps to address in dialogue. The ORCHID project has organized two workshops (in 2018 and 2019) with representative participation from stakeholder groups. Observations on the contributions and dialogue with participants from these workshops have been integrated into this guideline. Advice is tailored to stakeholder groups, taking into account that we are only at the start of defining a roadmap for OoC technology & application. Such guideline must be seen as a companion serving the research community to engage in a fruitful dialogue with stakeholders outside the core research community along the OoC technology & application roadmap.

Conclusions: Dialogue on ethical implications between the research community driving the technology & applications roadmap and the ecosystem, and stakeholders must be targeted to specific expectations, opportunities and risks for the different stakeholders. It must be timely and should be aligned with expected evolution of the roadmap.

3 The Research Community and their Stakeholders

In this chapter, we explore who is part of the Research Community of OoC and who are external stakeholders that should interact with the Research Community. It will become clear that the complex and interdisciplinary nature of OoC technologies, but also the diversity of applications proposed for OoC, results in a high complexity of managing mutual interests. Support from external stakeholders is essential to prioritize and drive the promising routes towards effective use of OoC technology. While the Research Community is maintaining high standards for the scientific communication of their achievements, guidelines may be helpful to define and entertain the necessary dialogue with the external stakeholders. In this dialogue the technology itself is often not emphasized, but the strengths and weaknesses of its use in an application, business or societal context.

3.1 The Research Community

OoC requires integration and use of a large variety of technologies at the crossroad of many different science and technology disciplines. In addition, users of OoC methods may draw on mature technology platforms as well as investigate novel technology tools to perform e.g. pharmaceutical or disease-related medical studies.



We define the Research Community as the group of research and innovation actors from academic institutions, research and technology organizations, clinical and industrial research departments. This community is already closely interacting on a scientific research basis across disciplines and across the academic-non-academic-clinical boundaries. Exponential increases in the number of publications and increasing numbers of patent filings are clear indicators.

Still, some challenges originate from such close collaboration and may benefit from guidelines: differences in affinity with end user applications, engagement with patients, ethical implications of experimentation, differences in intellectual property valuation due to disciplinary educational and training routes¹.

¹ OoC draws on a broad mix of technologies ranging from hardware over biologicals and reagents to protocols/workflows and software/algorithms. Non-recurring development cost vs production cost differ fundamentally for these different technologies as do IP protection and valuation practices.

3.2 Stakeholders

The OoC Research Community explores the use of OoC for a variety of application cases. Each application case naturally brings along a different set of external stakeholders. We assess several relevant use cases and analyze the stakeholder groups for commonalities.

We start from ORCHID's definition of OoC:



An Organ-on-Chip is a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ's dynamics, functionality and (patho)physiological response in vivo under real-time monitoring.

Organ-on-chip models are expected to result in a paradigm shift for healthcare leading to new ways to elucidate disease mechanisms, identify effective drugs and improve health by prevention and personalized cure of many diseases. As a result of market studies and two workshops, we have identified four healthcare-related application areas where OoC could have significant impact. The research community is active in all 4 domains.

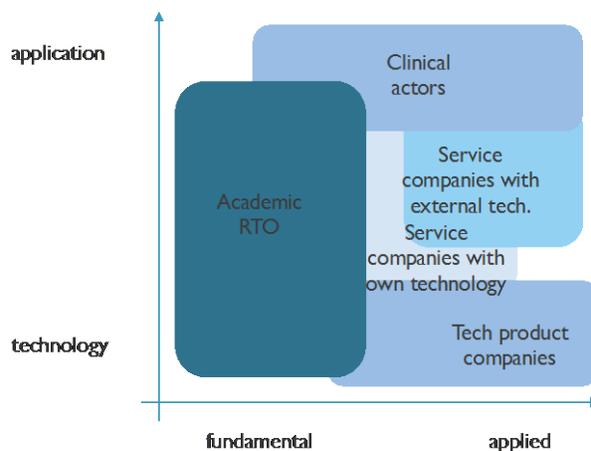
1. **Drug toxicity and safety testing:** The pharmaceutical industry but also cosmetics or chemical industries are major stakeholders in using OoC as a test tool. Safety testing obligations are legally issued and regulated by governmental or supra-governmental bodies including regulatory agencies. Government agencies support research and innovation, as well as the development of methods and standards, and also the development of alternative methods to animal testing. A.o. animal right activists appear as intermediary stakeholders for citizen groups. General media are much more inclined taking up this route since there seems to be an immediate positive benefit to society: the fact that it removes a present ethical burden, long-standing activism and the political ambition e.g. by the European Commission ²and European member states ³to look for alternatives (3R policies). The research community is active in developing OoC platforms and methods.
2. **Drug efficacy testing:** Among the end users the pharmaceutical industry is the major stakeholder, looking for better human test systems. Drug efficacy testing is a mandatory step towards admission of drugs. Test results enter the regulatory approval procedure for the admission of drugs by regulatory agencies. Government agencies support research and innovation and support the development of methods and standards. The pharmaceutical industry players themselves are looking for joint pre-competitive research on method development. The research community itself is an active player, often closely collaborating with the pharmaceutical industry. General media are not easily taking up this route, with drug efficacy testing being a somewhat hidden intermediate step in the drug development process.

² E.g. abolishment of animal testing for the cosmetics industry.

³ E.g. the political ambition in the Netherlands to be the world leader animal-free innovations by 2025.

3. **Disease mechanism modeling and understanding:** For this application area the pharmaceutical industry is a major stakeholder among the end users, but biomedical and clinical sciences are significant contributors. Government agencies but also private foundations support research into specific disease areas, either driven by broad population health challenges, specific healthcare needs, or alternative motivations. Patient organizations are an active intermediary stakeholder for patients. Access to specific patient panels is essential. General media are taking up this route in a moderate way, often highlighting the technological aspects.
4. **Personalized medicine:** Both the pharmaceutical industry and the clinical departments are major contributors. Use of tools and therapies requires regulatory approval. New approaches challenge governments and regulatory bodies for new legislation or interpretation of legislation. Both access to individual patients as well as to representative patient panels is essential. Patient organizations may be active as an intermediary stakeholder for patients. General media are easily taking up this route, linking it to advances in therapies. It also triggers business and policy-related media due to the translational link to the clinical practice and the patient/citizen.

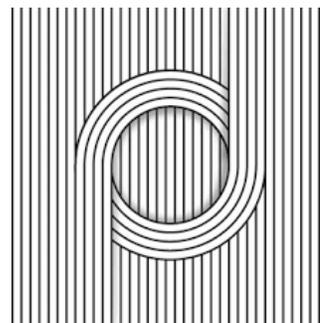
We intentionally omitted the technology industry in the previous consideration: Market analysis and interviews with major stakeholders have clearly revealed that all OoC technology presently available has emerged only recently from academic settings, primarily through start-up companies. They all still maintain a very close link to their academic context since the current market size is still limited. Technology R&D is carried out by the research community and an emerging group of primarily small and medium-size enterprises (SMEs) with dedicated, often proprietary OoC platforms. The most prevalent business model is the hybrid model offering OoC technology products as well as services in which the SME's own OoC technology products are internally used for service to customers. These SMEs are often closely embedded in the research community but could also appear as an external stakeholder, depending on the business model employed in a specific collaboration.



Industry as a technology provider may be considered a separate stakeholder once there is market size, product varieties are offered and/or volumes increase, and a more distinct value chain gets established. As seen previously in the life sciences technology, lab equipment and medical devices industries, this may kick off acquisitions by larger equipment builders and it may also lead to either quasi-standards by market dominance or to agreement on interoperability standards. Both would lead to a more independent position of technology providers.

4 Guidelines for the Research Community

In the previous chapter, we have given an outline of the Research Community and the stakeholders with whom they engage, intentionally or unintentionally. We also described the challenges of these interactions, ranging from terminology to differences in primary drivers. In this chapter, our aim is to give recommendations on how to structure a comprehensive and mutually beneficial communication with the various players in the surrounding ecosystem.



The scope of these guidelines is on facilitating dialogue on ethical implications. Section 4.1 starts with recommendations arising within the Research Community due to its interdisciplinarity. Follow-up sections 4.2 through 4.7 address interactions with external stakeholders.

4.1 Across disciplines within the Research Community

Recommendations:

- **Intensify collaboration around the common interest of OoC.** Build up OoC-driven, cross-disciplinary activities, networks, clusters, conferences, journals that foster mutual understanding and exposure to other disciplinary contributions. Build up a local anchoring for the significant number of European actors in the field. The establishment of EUROoCS, the European Organ-on-Chip Society, is a major step in this direction to anchor in Europe, but the global perspective with other active regions (primarily Northern America at this time) should not be neglected.
- **Invest in training across disciplines but also go beyond scientific training only.** Consider a combination of theoretical and hands-on immersive trainings with exposure to work flows and processes. Use the learning experience of concrete cases to develop in-take procedures, training programs and additions to curricula. The EUROoC ITN is taking up this challenge. Enlarge such trainings with non-technical components such as bioethics, data privacy, trial management, personal safety⁴.
- **Open the debate on viability and availability of open platforms** between research actors. Open platforms and open interfaces⁵ may reduce the entrance barrier for first users, but a suitable business model must be developed to sustain economic viability for those that contribute to the technology and thus to access for the research users. This requires a discussion on maturity expectations for e.g. platform components or technologies but also for cell sources or cell media.

⁴ Development and use of OoC technology require different disciplines with different safety practices to work with each other, e.g. across materials and infrastructures with different safety standards and expectations.

⁵ Note that the openness may reduce the entrance barrier, but it also allows customization by everyone. This may be counterproductive for qualifying the platform for specific purposes since it may evolve. This is a clear dilemma e.g. for use towards regulatory admission. Standardized and/or controlled qualified releases may be helpful.

4.2 Towards the industry as end user

In particular, for drug toxicity and drug efficacy testing, pharmaceutical and other industries with legal and regulatory obligations for product admission such as the cosmetics industry or the chemical industry are the main end users and beneficiaries. Technology is a means. Drivers are primarily business and market opportunities leading to a better competitive position (e.g. shorter time-to-market, lower development cost, better product performance) or the reduction of risks and potential liabilities (e.g. lower risk on side-effects of products), the latter being often imposed by law and managed by regulatory instances.

Recommendations:

- **Aim at understanding from the stakeholder how they can maximally benefit from OoC Engage in the discussion:** 3R principles may positively influence drug toxicity testing but it is not clear whether OoC shall be an actual replacement or an additional tool. For the drug efficacy route, it is important for OoC development to know whether lower attrition rate and thus lower overall cost or faster time-to-market is essential. Inform on burdens, e.g. related to regulatory acceptance of alternative methods and effort on qualification.
- **Seek for synergistic effects across multiple players.** Joint pre-competitive development of methods may benefit method acceptance and regulatory approval and fasten or simplify adoption. Use the momentum that large industries such as pharma can mobilize.

4.3 Towards the healthcare sector as end user and intermediary

The health system consists of a set of actors ranging from governments, their health departments, health insurance companies, to all actors in the clinical treatment process.

Recommendations:

- **Define priorities in clear application scenarios together with the value chain of health actors to focus investment. Balance investment into shorter-term targets and longer-term targets benefitting from a.o. the ORCHID roadmap.** Umbrella investments into *any kind of* OoC will mostly lead to scattered efforts. It is essential to convince government to invest in research and even more in innovation or in (pre-)clinical or translational studies regarding clear applications with mandatory support of the entire chain of health actors including regulatory partners.
- **Develop personalized medicine and therapy cases gradually with all stakeholders in the healthcare sector. Keep scalability in mind but do not expect a rapid increase in treatment numbers.** Personalized medicine in general and enabled by OoC in particular is revolutionary to nearly all established relations between healthcare actors. An early health technology assessment is absolutely mandatory, even to work out the tandem of technology platform and biology. Procedures for proper patient involvement and follow-up throughout the entire procedure from possibly early diagnosis, detailed disease diagnosis, optimum treatment plan using OoC for

therapy selection or even in combination with cell therapy need to be established. Personalized diagnostics and e.g. drug choice for therapy requires comparably little effort to start with the individual patient (requiring e.g. only material donation by the patient him/herself). OoC technology could be used to screen for the most efficient drug and thus therapy choice for the individual patient but the approach lacks a valid qualification and regulatory approval. It can be easily used in research or investigational use as an additional decision input by the clinician⁶. There is an ethical dilemma for the clinician on whether or not to use this approach and potential risks and liabilities involved. This approach is incompatible with existing regulatory practices and has no path when scaling up to larger patient populations. The business case and value for all parties involved still need to be investigated with governmental actors, health departments, health insurers, healthcare providers and the patients.

- **Inform and consult patient organizations.** It is easier to discuss needs but also to give a realistic picture to patient organizations than to individuals or through general media. Patient organizations may provide valuable links to patient groups. They also have a genuine interest in providing information on e.g. procedural burdens for treatments or privacy aspects of patients. They have some insight into actual success of existing therapies. This is particularly important for personalized medicine and therapies, where a momentum is seen today to engage into a better follow-up of patients in treatment with the promise of better health outcomes.

4.4 Towards governmental end users and intermediary regulatory actors

For regulated market access such as for pharmaceuticals but also for cosmetics or chemical substances, regulatory agencies act as intermediaries for governments. Governmental actors may also perform directly or indirectly through legislation or delegation, surveillance of risks identified (e.g. environmental monitoring, pollution monitoring, food product testing). There is a steady request to improve the repertoire of available qualified methods and procedures, but this relies on collaboration with the research community.

Recommendations:

- **Engage early with regulatory agencies assessing the need, potential and burden for new methods.** OoC methods are complex and in fact rather revolutionary as compared to e.g. animal models. Development and qualification of new methods is a big and possibly time-consuming investment. This requires a process of building trust and insight into the capabilities of OoC. Regulatory agencies see many parallel efforts and may be a valuable contributor to determining where synergies in method development would be helpful.
- **Assess at a global level how regulatory agencies look into new OoC methods.** Certainly, for an emerging technique, evolutions differ from nation to nation. Regulation may be inconclusive and

⁶ The use of life science lab equipment approved for research-use only as an additional decision input by clinicians is not an unusual route today, mostly when facing complex or rare diseases.

access to certain markets may still be denied for OoC techniques. Information exchange on such differences in evolution and ideally efforts for harmonization should be fostered. Regulators, industry sectors and the research societies should join forces here.

4.5 Towards decision makers in government and investors

It has become clear that few OoC solutions are truly low hanging fruit with off-the-shelf solutions for end users on the market tomorrow. It is essential that decision makers with the capabilities to pave a path to a product are well informed on the trajectory it takes with all stakeholders. Talking about decision makers, we address both governmental actors as well as (financial) investors. Today, hybrid public-private investments are common – either as joint investments into a specific innovation phase or sequential or as sequential cascades.

Recommendations:

- **Aim at more visibility and predictability on where OoC technology can go – how and by when.** The roadmapping process in ORCHID is a good starting point for this action. Complement this with socio-economic information, ethical, regulatory and standardization questions. This is an attractive menu giving perspectives to government decision makers as well as to investors for setting policies, societal and health goals and priorities, or deciding investment engagements. Manage expectations realistically – there is nothing worse towards decision makers than overpromising and coming back repeatedly with bad surprises. But also ask for the necessary critical mass and support since competition elsewhere never sleeps.
- **Invest into partnering for early health technology assessment (HTA) with experienced partners.** Decision makers in governments and investment know what to look for besides the plain technology information. However, the research community needs to develop own capabilities here in order to entertain a balanced dialogue: Partnering with existing HTA actors (service providers, sector organizations, government agencies, insurance companies) but also with specialized investors is probably the fastest route but it requires a two-way communication informing them on where OoC technology stands and understanding on where it needs to go in order to being positively assessed. Early HTA may reveal non-technological barriers, e.g. through lacking reimbursement schemes or incompatibility with established clinical procedure. Ethical dilemma's may be avoided that way: OoC technology that is halted after research because products cannot be timely deployed (opportunity window). OoC technology that is not developed since non-technological barriers are seen and not tackled (too narrow technology-only focus).
- **Request government actors to align on legal, ethical and regulatory aspects.** Today's market is a global market yet healthcare systems are still predominantly influenced by proprietary national systems. Incompatible requirements for market entry lead to loss of opportunities and unnecessarily high costs. It is important to inform government actors on these barriers. It is a societal choice with ethical implications which routes to enable and prioritize. But it is also important to inform government actors on when technology is ready and have them prepare the non-technical aspects such that the technology can be used when ready.

4.6 Towards the media as an intermediary

Media act as a mediator and catalyst to bridge towards different communities. It is important to note that for modern ICT technologies there is more and more democratized dissemination of information and access to information without a content editor as intermediary. This however brings the burden of properly addressing the audience and creating trust and authenticity into the hands of the content creator.

Recommendations:

- **Select appropriate scientific channels and build bridges:** Scientific peer review is an important criterium for quality. However, discipline-oriented societies, journals and conferences can prevent easy access and overview on the state-of-the-art. The currently promoted or even mandatory use of open access publications may facilitate better dissemination of OoC results across traditional disciplinary boundaries as established by disciplinary science societies or journals. EUROoCS as an interdisciplinary society should further build bridges here.
- **Feed and follow business or policy-related media:** Business and government decision makers are looking at OoC from a risk-benefit perspective but often need to make both quick tactical short-term decisions as well as strategic long-term decisions. Both will clearly benefit from a well-built and maintained roadmap as now being prepared by ORCHID. Side material documenting the build-up of such roadmap at hand will aid quick decision-making when opportunities come along. Roadmaps need to include foresight on scientific and technology evolutions but also translation into the required favorable side conditions.: support by e.g. governments, foundations, investors, intermediary organizations for specific OoC use through e.g. legal and regulatory agencies and investment incentives may hit the news. That can go hand in hand with offering information, training, showcasing early success cases and using the opportunity of the media to address various stakeholders specifically. Such non-technical aspects together with possible legal & ethical implications are a mandatory part of such roadmap. It is essential for OoC societies and networks to feed and follow these media.
- **Engage with general media addressing the public at large systematically:** As described in Deliverable D5.2 in more detail, general media are often indirectly triggered through other events such as press releases. A more systematic engagement, in particularly not only focusing on scientific novelty but also framing results properly is important to shape expectations in sync with reality. Societies and network organizations should be supportive here. EUROoCS should have a clear role here.

4.7 Towards the public at large

Direct dialogue with the public at large is particularly challenging given that the large public is often most distant from early research. The related analysis and forthcoming specific recommendations are provided in a separate Deliverable D5.2.

5 Conclusions

Dialogue on ethical implications of OoC technology between the research community driving the technology & applications roadmap and their ecosystem and stakeholders around must be targeted to specific expectations, opportunities and risks for different stakeholders. It must be timely and should be aligned with expected evolutions in the roadmap.

We notice big differences in time-to-use/market for various applications of OoC technology. It appears that applications with unknown, higher or more controversial risk potential (e.g. personalised therapies, digital twin) lie out further in the future, allowing for some time to build up the dialogue on ethical implications and address them gradually but in sufficient depth. For the applications with shorter time-to-market (e.g. drug and substance toxicity/efficacy), it is essential to follow-up on expectations closely. Communication on success cases is of utmost importance here but the pitfall of simple generalization and upscaling must be avoided.

Next steps: The guideline itself will be made available as public information material through the ORCHID website. Relevant action guidelines will be worked out more in depth with affected stakeholders. They will result in contributions to the overarching policy paper/Deliverable D5.6 proposing solution approaches for strategic non-technological challenges along the OoC roadmap and for specific milestones, i.e. focusing on communication with stakeholders, on ethical, legal/regulatory, and standardization aspects. A second concise primer/Deliverable D5.7 will address ways to advance adoption of OoC technology, also here along the OoC roadmap.

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