Toolboxes for the Advancement of Responsible industrial Technologies in Precision Medicine

The Industrial Dialogue workshops produced a number of proposals, which, to varying extent, put RRI principles into practice. The insight that responsible innovation depends on an ecosystem of diverse and interacting players has the consequence that tools for responsible innovation in industry are not confined to a discrete action taken within a specific company. Rather, it is in multi-stakeholder constellations that a company can cooperate with a hospital and a regulator to address a genuine societal concern. Because of this multi-stakeholder nature of RRI, participants proposed complex toolboxes, rather than individual tools. The following describes the proposals emerged in Aarhus and Valencia.

The data sharing toolbox

The tool in brief

This tool addresses the related challenges of data access, control and standardisation. Researchers wanting to access medical data for research often face three hurdles, a group of participants in the Aarhus workshop found. Firstly, much of the existing data is poorly visible, leading to biological samples (or digital bits) in biobanks and data repositories not being exploited properly. Secondly, the collection, storage and sharing of medical data is covered by complex regulations that are often nationally idiosyncratic. Thirdly, some companies have amassed impressive collections of medical data, but fail to grant open access to third parties, be it for business reasons or lacking awareness that the data might be of value for them.

How does it work?

The tool proposes a service infrastructure for data sharing to overcome these obstacles. Its foundation is a registry analogous to the Register of European Biobanks (BBMRI), acting as an inventory that lists data stores under the control of or created by industry, the public sector and public-private consortia. It empowers researchers from public as well as industrial organizations to quickly find out what data exists and if it can be accessed. This 'database of databases' should list different kinds of data, including aggregate data and

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data from failed trials, and enable their access and interoperability (i.e., make different standards and formats compatible).

Sharing data for medical research, the designers of this tool maintain, is ethically desirable if done in a socially responsible way, as it prevents the duplication of efforts and contributes to a culture of open access. Ethical data sharing, however, cannot be achieved without a clear governance framework. The data sharing infrastructure therefore has to raise awareness among its users about what laws and regulations apply to handling and sharing medical data, offer guidance in navigating the relevant and often complex regulations (e.g. which kind of permit is required from what agency), and provide formalized data sharing agreements. But responsible data sharing isn't defined by access alone, researchers also have a responsibility to make their own data open access and feed them back into repositories like the one discussed here, which might be encouraged through support in how to design a study that meets open access specifications.

Key requirements and open issues

Such a data sharing infrastructure cannot be set up responsibly without a societal license, its designers further maintain. It has to operate in a transparent manner so as to inspire trust by the general public as well as by the patients and research subjects that consented to their data being stored to foster research and innovation. Several measures were proposed to create legitimacy. Firstly, people who donate data should have control over how this data is used. There are current efforts to implement dynamic forms of consent which let donors approve individual requests for inclusion of their data in a particular study, rather than having data donors sign the equivalent of a blank cheque. Secondly, transparency can be fostered by recording who accesses the database, with what intention, and, further down the road, with what findings. Thirdly, the data sharing infrastructure could serve as a vehicle to sensitize its users about what responsible research and innovation is, why it matters and how it could be integrated into their research and development activities. Finally, putting the data sharing under governmental oversight might further strengthen its legitimacy.

If successful, such a data sharing infrastructure would generate a stakeholder community from different areas of society, be it academic researchers, companies, medical professionals and patient interest organizations. This diverse community will likely generate fresh ideas for researchers and innovators to build on. The infrastructure could be instrumental in sharing such ideas and enabling novel collaborations.

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There is no business plan yet for how to operate such a data sharing infrastructure and the workshop didn't provide enough time to go into such depths. However, the designers highlighted a number of concerns that need to be addressed, such as how to create buy in from existing public and private biobanks, how to convince physicians of its utility, and in which jurisdiction to house the infrastructure.

Decision aid for personalised medicine treatments

The toolbox in brief

In addition to biomarkers like genomics, precision medicine should also take into account a patient's subjective experience of illness and treatment, a group of participants highlighted. Effectively treating a mental illness like bi-polar disorder is notoriously difficult. Finding the right medication and dosage is a lengthy and highly personalised process that also involves adjusting for side effects. Given the choice, patient A might choose the drug that might be slightly less effective, but minimizes weight gain as a side effect. Patient B might care less about weight gain, but would not take a drug that affects sleep. And patient C might find that talk therapy offers a more meaningful life than a drug that stabilizes mood swings while at the same time numbing their experience of the world. The tool helps to facilitate this process and provides for an infrastructure to record and share lessons learned in the process.

How does it work?

The tool improves the traditional doctor-patient relationship in two ways. Firstly, what treatments are available to a patient in practice has as much to do with the health insurance system and the hospital management as it has with the treating physician's awareness of treatment options. Building and continuously refining a catalogue of treatment options independently of these gatekeepers expands patient choice, and by extension the degree of personalization. Secondly, the treatment experience of one patient might help the treatment of another if treatment choices and experiences are systematically documented and shared rather than kept within the bounds of the therapeutic relationship. To overcome this equivalent of an information silo, the proposed tool would include a secure database that, conditional on a patient's consent, allows such information to be recorded (possibly by

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patients from their home) and anonymously shared with interested doctors, researchers, patient groups, and other actors having a stake in the future improvement of treatment.

Key requirements and open issues

Patients benefit from the tool as it facilitates their engagement in the treatment process. General practitioners might not be keen on sharing information on their interaction with patients, especially in the Danish context where there has been a controversy around patient data that left doctors polarize on the issue. Nonetheless, the tool's designers insist that it offers value to general practitioners as well as hospital doctors, because better informed patients would be more engaged and thus more likely follow through with the treatment, rather than to just receive a prescription they fail to follow. Finally, industry and other researchers would benefit from this new data source.

To set up the tool, stakeholders of one particular disease area (e.g. bi-polar disorder) could come together to discuss how to concretize this idea. It might not be feasible to have a running system in 6 months, but concrete guidelines could be developed within this timeframe. Privacy and data ownership legislation regulating phase IV clinical trials could offer lessons as to how this new type of data could be treated. In addition, there could be a reporting requirement as to how and for what this data is being used.

Accreditation toolbox

The toolbox in brief

Participants in the Aarhus as well as the Valencia workshop developed strikingly similar versions of an accreditation tool; they are presented here in a single, merged version to avoid redundancy. The accreditation tool builds on the assumption that research organisations in the public and private sector, and health care facilities like hospitals can acquire trust and legitimacy through an established market of accreditation. Holders of the accreditation might be able to capitalize from it as their products and services become more trustworthy and could claim a higher market price. Further, funding agencies could give preferential treatment to certified organisations.

How does it work?

The accreditation would require certified organisations:

- To provide proof of adhering to standards of scientific quality and integrity (e.g. proof of a ring test laboratory qualification).
- To provide documentation of social and environmental impact.
- To document their communication and lobbying activities in a transparent manner.
- To include an ethical/social advisor in the company's project teams.
- To share data with 3rd parties where possible and to disclose negative results.
- To participate in multi stakeholder RRI working groups.
- To periodically administer a quality feedback survey among the end users of its producers and take action on the findings.
- To provide training and continuous education to its employees related to responsible innovation.
- To participate in transdisciplinary collaborative projects.
- To staff key departments with genetic specialists and counsellors; to routinely solicit feedback from their patients (only applies to hospitals).

Key requirements and open issues

- The accreditation would be delivered by an organisation which has a clear internal division of competences between an oversight body that defines content and an operative branch which grants certification.
- The accreditation would receive its authority through oversight by a members' council that includes well established health policy organisations (e.g. the European Medicines Agency, the European Board of Medical Genetics, etc.) alongside representatives from medical professions, research organisations, companies, and patient advocates.
- The accreditation should be updated periodically.
- The results from accreditation audits should be made public.

Living lab

The toolbox in brief

This tool takes up the challenge of implementing a multi-stakeholder approach to innovation. A Living lab is a space where different stakeholders can meet to jointly identify societal needs for health technology innovation and to work toward concrete innovation

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projects. As stated earlier, the European Commission believes that new organisational models can improve the effectiveness of the innovation process and lead to products and services that better meet society's needs and expectations.

How does it work?

The living lab has two goals: 1) to increase the efficiency of the research and innovation process, and 2) to guide the development trajectory of precision medicine by considering societal needs.

The living lab should encourage the collaboration between different stakeholders. A civil society organisation, for instance, could help define priorities and concrete projects. A small company could use the space to look for commercial partners that could support and finance a project. And a university researcher could apply for grants allocated through the lab, based on criteria of societal desirability. Beyond these stakeholder-specific instruments, the living lab establishes a community involved in product design and stage-gating innovation processes.

A precision medicine treatment protocol based in RRI principles could be an initial project for the living lab, a process that would require repeated interactions between the involved parties.

Key requirements and open issues

Collaboration has costs, whether it takes place in a physical or virtual space. The financial model to cover them remains open, but should revolve around a mix of public and private funds.

Communication toolbox

The toolbox in brief

Treating complex clinical cases requires that different actors like the general practitioner, the radiologist, the neuro surgeon, the care staff, and the hospital case manager communicate with each other. This need to coordinate activities will only increase with precision medicine. But precision medicine will not only affect how medical professionals interact. The treatment information that patients are exposed to will likely become more complex as treatments become more individualized. Companies offering health care products and services have a

responsibility to provide accessible documentation that reflects the state of the art of precision medicine.

How does it work?

A group of participants in the Valencia workshop proposed the following measures:

- Hospitals should set up a pharmacogenetics department that acts as an interface between the different hospital departments to foster proper (genetic) companion diagnostics and a more effective stratification of treatment.
- An industry association could act as a gatekeeper for reliable product information by offering special visibility on its website to those companies who have a proven track record in terms of quality and social responsibility. This website could offer target group specific information in order to take into account the different information needs and expertise of patients and doctors.
- Marketing departments of pharmaceutical companies would be required to provide information about whether their product works for all patients with the relevant indication, or only a subset thereof (i.e., stratification). A traffic light system would be implemented on the packaging of a drug with green standing for general efficacy for the entire population with the indication, yellow indicating a moderate stratification effect, and red requiring a companion diagnostic to determine if the drug would work at all. This information would also be shared with doctors via sales representatives.

Key requirements and open issues

- The position of a pharmacogenomics specialist builds on existing organizational models implemented in hospitals to coordinate across specialities.
- The traffic light system to indicate the degree of stratification of a drug will have to draw on a list of known biomarkers that have been vetted and approved by a central agency, such as the European Medicines Agency, or the US Food and Drug Administration.