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Communication

Multi-country stem cell trials

The need for an international support structure

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Introduction

Regenerative stem cell research is now rapidly moving toward the clinic and routine medical applications. With the number of Phase II and III trials growing, the conduct of multi-country clinical research collaborations is becoming increasingly important. These partnerships accelerate processes of clinical translation, and form the basis for marketing approval of new therapies in multiple countries (Martell et al., 2010). At present, however, the conduct of international stem cell trials is hampered by a high level of regulatory heterogeneity across countries, and the absence of internationally harmonized governance frameworks (Bubela et al., 2014). Even though drug regulatory authorities in the USA, the European Union and Canada have now initiated collaborations that focus on the convergence of regulatory procedures for cellular therapy products, globally harmonized regulatory procedures are far-off (Arcidiacono et al., 2012). Japan for instance, has recently introduced a fast-track approval path for stem cell therapies (Cyranoski, 2013), and in China and India drug regulatory agencies have at present only issued provisional regulations and regulatory guidelines whose legal power is limited (Sleeboom-Faulkner and Patra, 2011; Viswanathan et al., 2013; Rosemann, 2013). But complications arise also from the ongoing growth of unregulated stem cell treatments that are offered to patients without systematic proof of safety and efficacy in many countries (Lysaght and Sipp, 2014; Ogbogu et al., 2013). Lucrative business opportunities and the existence of regulatory grey areas have given rise to

uncontrolled applications and the emergence of transnational entrepreneurial networks that advocate alternative forms of research regulation. Professional associations such as the International Cellular Medicine Society (ICMS), for example, have developed their own guidelines and IRB and accreditation services (Blasimme, 2013). These activities support experimental for-profit interventions with stem cells outside of the methodological format of the randomized controlled trial and independent from the review procedures of drug regulatory agencies (Rosemann, under review). This diversification of clinical research standards within and across countries makes efforts of international harmonization increasingly difficult.

In Part I of this paper I will introduce four central challenges to the organization of international stem cell trials that emerge from this high level of regulatory variation. These obstacles apply in principle to all innovative multi-country stem cell trials that are subject to approval by a drug regulatory authority, including trials with (minimally manipulated) autologous stem cells. These challenges are especially pronounced, however, in the case of trials with pluripotent stem cells that involve increased technical complexity and higher risks for patients. Exceptions are trials that involve established stem cell treatments (such as the use of hematopoietic stem cells for leukemia), or studies that make use of autologous stem cells that are less than minimally manipulated and not subject to regulatory scrutiny (Li et al., 2014). Then in Part II I will argue for the need of an international support structure that systematically addresses these problems. In this regard, I will introduce five measures that may help to reduce existing difficulties and to conduct international stem cell trials in a more effective and cost-efficient way.

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Challenges to the organization of multi-country stem cell trials

A first challenge to the organization of multi-country stem cell trials is the necessity to conduct long-term in-depth research into the regulatory requirements of drug regulatory authorities in multiple countries (OECD, 2011). Stem cell therapies, as pointed out by Martell and colleagues 'do not neatly fit into current regulatory categories', and the barriers of translating stem cell-based approaches in functioning therapies lie 'in both technical and regulatory constraints' (Martell et al., 2010: 451). Regulations for the clinical use of stem cells are in many countries emerging only gradually and far-reaching regulatory differences exist. For clinical investigators and industry this diversified and rapidly changing situation is confusing and poses significant organizational difficulties (Rosemann, 2014a). What is required is a long-term, reflective engagement with the review and approval procedures that are handled by the drug regulatory authorities in the countries in which a trial is conducted. In order to develop study protocols that are compliant with the demands of multiple regulatory agencies, gaps between jurisdictional frameworks must be identified at an early stage of the clinical translation process. This is a difficult task that takes time and may be complicated by language barriers, insufficiently defined regulatory procedures, cultural differences and disparities in the enforcement of regulatory protocols (Ravinetto et al., 2013). It is complicated, furthermore, because the regulatory issues that are associated with the development of autologous stem cell therapies (Hourd et al. 2014) do in important respects differ from the characteristics that need to be taken into account in the context of clinical trials with pluripotent stem cells (Andrews et al., 2014).

A second challenge is that the interaction with medical authorities in multiple countries is resulting in a very high level of organizational complexity (Minisman et al., 2012). To file applications at multiple drug regulatory agencies is a time, cost and labor-intensive process that requires specially trained staff and a well-functioning administrative infrastructure (Rosemann, 2014b). While for industry-sponsored trials this is not necessarily a problem, for academic research groups and small-to-mid size biotech companies (which at present are the main sponsors of clinical stem cell trials) these resources are often not available and difficult to acquire (Keirstead, 2012).

A third type of challenge are time delays, increased costs and uncertainties that arise from non-existent or still emerging regulatory procedures in some countries. In China, for instance, where effective regulatory procedures for the clinical testing of stem cell-based therapeutic approaches have until 2012 been non-existent, the China Food and Drug Administration (CFDA) has repeatedly refused to accept incoming investigational new drug (IND) applications for stem cell-based products (Rosemann, 2013). Such unresolved regulatory issues can cause long-drawn-out delays and additional costs to the sponsors of clinical stem cell trials, and result in the need to apply for regulatory approval in another country where regulatory procedures are clearer, and to conduct the trial there (Bhagavati, 2014). But unresolved regulatory issues and the potential for sudden regulatory changes exist also in countries with highly developed regulatory frameworks. Noteworthy is, in particular, the ongoing debate

on who should regulate autologous stem cell interventions (Zarzczyński et al., 2014). In the USA, for instance, think tanks are using the case of autologous stem cells in order to promote broader deregulation and several companies and professional societies (most prominently the ICMS) have argued that 'autologous cell products should be treated as part of medical practice and thus not subjected to marketing approval' (Bianco and Sipp, 2014). These calls have resulted in a bill for the Freedom of Choice Act that was put forward to the US congress in April 2014. According to this bill investigational stem cell technologies could be sold to terminally ill patients, outside of the control of the US Food and Drug Administration (FDA) (Morgan, 2014). Similar developments can also be reported from other highly regulated countries. Australia, for instance, has exempted autologous stem cells from the review procedures of its drug regulatory agency (Tuch and Wall, 2014) and in Italy the use of autologous mesenchymal stem cells has been taken out of the jurisdiction of the Italian Medicine's Agency in 2013 (Berger et al., 2014). These developments are likely to influence regulations in other countries (Bianco and Sipp, 2014). Most importantly, however, the jurisdictional variation in regulatory frameworks and the prospect of ongoing policy changes make the implementation of multi-country stem cell trials more difficult and increase the risk of organizational complications, unexpected or misplaced investments and time delays.

A fourth challenge is that the high level of regulatory variation across countries necessitates far-reaching forms of scientific self-governance, training and procedural adjustments in participating clinical trial sites (Rosemann, 2014b). A central reason for this is, that the existence of regulatory differences between national jurisdictions is reflected in contrasts of clinical research practices and methodologies, at the level of local medical institutions. In many countries, moreover, knowledge on the conduct of systematized controlled stem cells trials is often limited among clinical researchers (Li et al., 2014). These disparities between and also within local hospitals form a clear threat to the scientific integrity of international stem cell trials (OECD, 2011). As a result, intensive forms of staff training and adjustments of local clinical research practices are necessary, so that standardized research protocols can be implemented (Ravinetto et al., 2013). Standardization requires, furthermore, the implementation of reliable monitoring and control infrastructures. For academic investigators and small-to-mid size companies the performances of these tasks pose a significant organizational and financial burden (Keirstead, 2012). Unless sufficient funding for these forms of education and scientific self-governance is acquired, multi-center international stem cell trials cannot be conducted.

The need for an international support structure

The International Society of Stem Cell Research (ISSCR) has in 2010 called for the need to harmonize regulations for the clinical translation and commercialization of stem cell-based products and therapies (Martell et al., 2010). However, in 2014 the global regulatory landscape for clinical stem cell research remains as diverse as before. This situation continues to pose problems to the organization of transnational stem cell trials. What is needed in order to improve this situation is

the creation of an international support structure, through which the organizational challenges of multi-country stem cell trials can be systematically addressed. International bodies such as the ISSCR or the International Stem Cell Forum have until now focused primarily on the development of guidelines, best practice standards and various types of recommendation. These documents have concentrated on crucial aspects of the clinical translation process, including the collection, derivation, storage and clinical application of stem cells, as well as intellectual property rights, commercialization, industry engagement and ethical issues of stem cell research (Isasi, 2012). However, a support structure that specifically addresses the regulatory and organizational challenges of multi-country stem cell trials has so far not yet been developed. Such a scheme could encompass five elements:

1. The development of a web-based databank that provides detailed information on regulatory requirements and procedures for clinical stem cell research and marketing approval in a large number of countries.

This repository could provide a detailed overview of responsible government units, key contacts, as well as regulatory documents and websites. Regulatory procedures and manuals on how to apply for and conduct stem cell clinical trials in different countries could be introduced in detail. This databank could work with a computerized system that explains differences between the regulatory requirement of specific countries and regions, and that helps to clarify what kind of tasks clinical trial sponsors will have to perform to balance out these regulatory gaps. In order to be valuable, such a database would have to be nuanced for different cell types and manufacturing standards. It would also have to provide information for the regulation of combination therapies (such as cell therapy-drug or cell therapy-device) where different regulatory pathways are required for each element.

2. The establishment of an international task force that identifies the central challenges to multi-country stem cell trials.

This task force could consist of researchers and sponsors with experience in the organization of multi-country trials. It should strive for the identification of the key challenges for the clinical translation of stem cell-based therapies in the context of international projects. Such a task force could aim, furthermore, for the development of solution strategies through which international stem cell trials can be conducted in a more time and cost efficient way. These measures could include, for example, information packages for sponsors and clinical investigators, as well as tools for staff training, project management and data collection. Such a task force could be initiated by the ISSCR, the International Stem Cell Forum (ISCF), or another international society such as the International Society of Cellular Therapies (ISCT).

3. The creation of an interactive online education and discussion platform.

The establishment of an interactive education and discussion platform would allow for the sharing of critical

information and experiences of clinical trial sponsors and investigators. Scientists or sponsors who plan to conduct international stem cell trials can learn in this way from the experiences of other researchers, and make practice-based assessments of the tasks, costs, timeframes and challenges that may lie ahead of them. Such knowledge could also help to make well-informed budgetary estimations, and to gain access to other useful information such as information about insurance schemes, the implementation of project-internal monitoring systems, and ethics committee approval (Ravinetto et al., 2013).

4. Raise awareness of the challenges of multi-country stem cell trials among public, private and charitable funding bodies.

To facilitate international collaborations in the stem cell field, it will be important to create an awareness of the challenges of multi-country stem cell trials among public, private and charitable funding bodies. To develop an understanding of these problems it will be crucial to prevent unrealistic expectations, and to obtain additional money that is required to tackle the challenges associated with international stem cell trials. A first step into this direction has been made by researchers at the University of Alberta in Canada, together with colleagues from McGill University, the University of British Columbia and the London Regenerative Medicine Network (Bubela et al., 2012). This group has founded the interactive online forum 'Enabling Advanced Cell Technologies (EnACT)' [<http://enactforum.org>], that offers an interactive, moderated discussion platform that aims to develop 'solutions to key non-science barriers' to the clinical translation of cell and stem cell-based treatment pathways (Bubela et al., 2012). The EnACT website features twelve thematic areas where barriers to translational stem cell research emerge. However, the challenges for the organization of multi-country clinical trial collaborations are not discussed on the forum. Moreover, online forums may not be the best way to identify and/or raise awareness of the challenges of international stem cell trials. The organization of a series of workshops and publications that could be organized by the ISSCR, the ISCF, the ISCT or another professional organization promises to be a more efficient method. Ideally, such workshops would involve representatives from public as well as charitable funding bodies, the industry and drug regulatory agencies from multiple countries.

5. Promote forms of regulatory harmonization and lobby for better communication between drug regulatory authorities.

A final field of activity would be the promotion of forms or regulatory harmonization or at least, to lobby for better communication between drug regulatory authorities, so that some of the challenges regarding multi-country stem cell trials can be prevented or reduced. Harmonization, as recently pointed out in a position paper of the US FDA's Office of Cellular, Tissue, and Gene Therapies, does not necessarily imply the production of internationally shared consensus guidelines (as in case of the ICH-GCP standards). Harmonization can refer too to the partial convergence of regulatory perspectives—but based on

the independent development of national regulations and guidelines (Arcidiacono et al., 2012). In light of the current level of regulatory divergence in the clinical stem cell field, it is questionable whether such a convergence perspective could really be achieved. Be this as it may, considering the existing challenges for the performance of international stem cell trials, the move toward a more coherent and predictable international regulatory landscape would clearly be advantageous.

Conclusions

While there is little doubt that the introduction of such an international support structure for multi-country stem cell trials would be of great value, its feasibility must be viewed from the perspective of possible sponsors. Considering the high costs of clinical translation it is to be expected that the greater part of Phase III trials will involve commercial sponsors. A newly devised support structure, therefore, must be of use to both academic investigators and corporate sponsors. Ideally, representatives of both groups will be involved in the design of these measures. It is not unlikely though, that commercial sponsors may prefer to undertake their own work into the regulatory barriers of international stem cell trials, for instance by external regulatory affairs consultants that help companies to navigate and identify existing challenges. For fear of competition these corporations may not be willing or able to share this information through online forums, publications or other means. At present, however, the majority of clinical trials in the stem cell field are either investigator-initiated or trials that are organized by small to mid-size biotech companies, often startups that operate under high risks. The financial means of both of these groups are usually limited. Moreover the time and organizational capacities—especially of academic investigators—are highly restricted. For these groups a support structure in which many of the question and practical challenges that emerge in the context of multi-country stem cell trials are discussed and anticipated will allow to save costs, time and facilitate realistic assessments and planning. A problem is, of course, that such initiatives are likely to be expensive. The organization of such a support structure should best lie in the hands of an international professional society such as the International Society for Stem Cell Research or the International Society of Cellular Therapies, which are large scale organizations that represent large numbers of researchers in many countries and that also cater the interests of the industry. Alternatively, the International Stem Cell Forum—which brings together some of the main public funding bodies for stem cell research around the world—would be a suitable umbrella organization for such an initiative. These organizations are firmly grounded into the international scientific community and have a high level of credibility. Most importantly, they are most likely to reach a large number of interested stakeholders and it also is in the interest of these institutions to provide up-to-date information, to stimulate participation and to disseminate findings from such an initiative. These large international organizations are also in the best position to attract the funding for such a transnational support structure, and to provide an apposite organizational platform. Considering the high expenses and financial risks of

multi-country stem cell trials and the potential for regulatory misassessments and long-drawn-out delays, the money for such an international support structure seems well invested.

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