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Clinical Research: Access to Potential Participants Pre-Enrollment: Staying One Step Ahead?

Inserm Ethics Committee

"Research with Direct Access to Patients" Group

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Summary

At the World Economic Forum in Davos, the CEO of Novartis had declared that the sources of innovation were found in digital solutions, particularly those concerning clinical trial enrollment. In a world in which research is competitive, having access to patients is critical, essential and inescapable. The stakes, therefore, are high.

Any organization of a clinical trial able to facilitate patient enrollment will enable faster, more reliable and probably more representative responses to the questions being studied. An undeniable advantage when it comes to addressing patient needs faster and better, and in cases of rare diseases can even be a necessity.

We consider the enrollment process to have two distinct phases. One is formal and strictly supervised, at least in France, in which the investigating physician explains the research, invites the patient to take part and, if they accept, obtains their written enlighten consent. The second, which occurred first, less formal phase involves identifying a potentially eligible and interested individual, providing them with informal information about an existing protocol and, if they agree, referring them to the investigating physician. In traditional clinical research organization, this pre-enrollment phase is generally handled by the investigators themselves and the two phases under the responsibility of the same actor. With the new technologies offering patients more choice, it is our hypothesis that other players could set their sights on the upstream phase and as such influence the directions that patients take.

Therefore, the key question is: in the future, how will protocols be chosen and the participants informed?

At this stage in the enrollment process, we consider it essential and urgent both from a methodological and ethical point of view to continue to educate patients about what research is and means. Patient associations play and will continue to play a critical role in that – something that the pharmaceutical companies and some academic researchers have already understood and taken into account.

Healthcare information and communication technologies are likely to transform not just the treatment, screening and prevention of diseases but also the performance of clinical research. The possible scope of impact is vast and as such we have chosen to focus on clinical research within the limited scope of affected patients, thereby excluding research on healthy volunteers and in the areas of prevention or wellbeing (sleep, performance, etc.). To narrow it down yet further, the example chosen for our reflection is that of a drug test (most often a clinical trial sponsored by a pharma, but other scenarios are possible). Our analysis generally therefore concerns research on humans with a view to developing biological or medical knowledge: interventional research, drugs research.

At the World Economic Forum in Davos, Novartis CEO Joe Jimenez had declared that the sources of innovation were found in digital solutions, particularly *concerning clinical trial enrollment*… the costs and quality of these trials and the real time analysis of data: "We can meet our patients in the digital world"[1]. The report by consulting firm Deloitte: "A new future for R&D? Measuring the return from pharmaceutical innovation 2017"[2] is also quite enlightening. While this report notes a decreased return on industry investment over the previous seven years, the use of new technologies (connected objects, social media, artificial intelligence, etc.) is considered to be a source of profit increase. *The possibility of online enrollment is explicitly mentioned on page 25.* While this scenario is impossible in France for legal reasons, the steps prior to enrollment, whose aim is to promote that enrollment however deserve closer examination.

Anything that encourages the recruitment of patients into clinical trials and anything that is likely to impact this process in one trial rather than another, deserves to be known, analyzed and understood. The stakes are high because in a world in which research is competitive and a source of profit, accessing patients is a critical, essential and inescapable step. The aforementioned Deloitte report refers to the over 1,000 trials ongoing in cancer immunotherapy – for which there are simply not enough eligible and accessible patients to go around (Deloitte report, page 6). Accessing patients is therefore a matter of major importance.

For industry, getting answers quickly thanks to large numbers of rapidly mobilized patients means longer periods of monopolistic situation for the resultant drug (without competition from generics). The speed at which this is done – which partially depends on recruitment methods, minimal losses to follow-up and the rapid constitution of the reimbursement application – is also key. For some drugs, 12 weeks saved represent an additional $800 million for the

[1] https://accuprecnews.wixsite.com/blog/single-post/2018/01/28/3-things-that-will-change-medicine
[2] https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/measuring-return-from-pharmaceutical-innovation.html

company (Deloitte report, page 26). More cynically, the rapid enrollment of a large number of patients is one way of asphyxiating competitors. An economic player in a position of dominance can, by delaying the emergence of competitor innovations, prolong their more or less monopolistic position.

These “Research & Development” stakes are so high that alongside traditional research in which “privileged” access to patients is targeted, other types of alternative research involving humans are undergoing development (not discussed in this document), such as virtual trials, parallel or nested trials.

Civil society has a legitimate interest in questioning the potential impacts of this type of change occurring in clinical research. It is our sentiment that such a transformation justifies ethical reflection because of the scientific, social and economic both benefits and risks are involved.

Clinical research projects with direct access to patients exist already, at least in the USA(1), and with online consent (Barrera 2017). A model not discussed here, even if the competitive “dumping” hypothesis should not be ruled out – with pharmaceutical companies able to choose to localize research projects in countries whose legislation authorizes this type of research.

Our discussion concerns the upstream steps: before enrollment in a research project is formally proposed to the patient. Indeed, some eligible (and ineligible) patients can be informed of the existence of such projects by many channels conveying more or less structured information.

For example, the March 2018 issue (No. 134, p.25) of the France Parkinson (patient) association journal *L'écho* contains a section called *Fox Trial Finder : un outil pour la recherche clinique* (Fox Trial Finder: a tool for clinical research). The association encourages its readers – mainly patients and their loved ones – to visit the https://foxtrialfinder.michaeljfox.org website in order to access the list and details of trials in France and worldwide. On this site, users having created their anonymous profile can access the list and details of the studies in their region and receive *notification of each new study* added. They also have the ability to dialog with or be contacted by a study center via secure messaging with the promise of guaranteed confidentiality.

We consider it necessary to raise awareness of the significance of these changes and their consistency with the principles regulating clinical research legitimacy.

BENEFITS

The benefit of direct access is to facilitate enrollment at least in quantitative terms (2) and thereby enable faster, more reliable and probably more representative responses to the

questions being studied. *It is an undeniable advantage and in cases of rare circumstances and diseases can even be a necessity.*

Only half of clinical trials succeed in achieving the desired levels of enrollment[3] and recruitment issues remain the leading cause of premature trial discontinuation. Furthermore, the “Right to Try” debate highlights that limitations of access to clinical trials rank higher than patient preference when it comes to low participation rates. Resolving this issue is therefore key from both the scientific and economic viewpoints.

An added value of these procedures is to enable patients who are relatively remote (in geographical or information access terms) from the study centers to access these trials. However, what they do not resolve is the issue of cultural distance. Concerning this important point, patient interface tools are currently being developed, under the partially structured and coordinated influence of companies, doctors (and learned societies), patient platforms (PatientsLikeMe), patient associations and individual initiatives.

Some structures dedicated to clinical research, such as Contract Research Organizations (CROs) – interfaces between pharmaceutical companies and patients, have hired linguists/anthropologists to facilitate uniformity of research across the various countries concerned[4].

These necessary and commendable efforts should be the subject of medium and long-term evaluations, as the evident interests of the sponsors of these tools could generate bias. Indeed, it is usual to consider that the construction of questions makes it possible to guide the answers (anchoring cognitive bias, tendency to answer yes more often than no…). Controlling the questionnaires can as such guide the responses.

[3] One such CRO, Chiltern, was recently acquired by Labcorp for 1.2 billion dollars.
[4] Personal communication with a representative from the company MAPI

ADJUSTING BALANCES AND POTENTIAL CONSEQUENCES JUSTIFYING RECOMMENDATIONS (RISK ANALYSIS)

To favor an analytical approach we will imagine the potential modifications according to a chronological sequence similar to the theoretical construction of a research protocol. For simplification, the current context is described under the heading *Today* and how we imagine research with pre-enrollment direct access under the heading *Tomorrow*.

PROTOCOL DRAFTING

Today: the sponsor (company, academic institution or association) chooses the disease it wishes to study, the type of intervention and test molecule, and then prepares the study protocol. At present, civil society does not get involved in regulating this step, unless for incentivizing purposes, such as for economic and financial rules regarding orphan diseases or orphan drugs. When patient associations such as AFM or non-profits such as the Drugs for Neglected Diseases initiative (DNDi) embarked on clinical trials, they complied with the currently applicable social rules and technical procedures and adopted their steps and methods.

Tomorrow: it is highly unlikely that this step will change in the future unless patient associations, in partnership with companies – in fact in a power struggle and context of information asymmetry and/or dependency – construct the targets, tools and protocols together. This process is already underway (for example, the partnership between PatientsLikeMe and Denali Pharmaceuticals) without it being possible to analyze in a simple way the resulting strengths and interests.

UPSTREAM INFORMATION PHASE (PRE-IDENTIFICATION OF THE PATIENTS, CONTACT, PRELIMINARY INFORMATION)

This is the phase in which the most changes are expected.

Step 1: contacting potentially eligible patients (target with a more or less important halo surrounding the target)

Today: contacting the individuals, informing them of the existence of a protocol and then informing them of the nature of that protocol are done by one main player: the investigating physician (and its team). The general information and participation proposal steps are both therefore handled by the same player, sometimes at the same time.

Tomorrow: we can imagine (and sometimes already observe) multiple channels used to identify and contact potential patients.

- Publicity (non-targeted) with a specific message: “Ask your doctor for advice, consult the ... website”
- Patient groups with specific diseases or symptoms, which can be targeted through:
    - patient use of mobile applications,
    - patient use of websites such as PatientsLikeMe[5], 23andme and Ancestry,
    - patient associations,
    - the identification of “targets” via algorithms analyzing social media, such as Facebook (2). The analysis of voice frequencies during telephone conversations or the analysis of the use of touch screens (such as that of a cell phone) already make the early diagnosis of Parkinson’s disease possible. The analysis of journeys via geolocation enables the detection of orientation disorders that are highly predictive of Alzheimer’s disease. While these elements are more or less in their very early stages and to our knowledge unused, they are examples of identification tools. The recent entry into force of the EU General Data Protection Regulation (GDPR) is meant to guarantee the protection of individual data and more particularly health data. This regulation is supposed to include any practices once a European citizen or location is concerned. All that remains is to find out how such checks could be conducted effectively[6].

Patients with a disease whose treatment so far is insufficiently effective can also look online to see whether research protocols exist, in which case they would be directed to the company’s website by the (more or less neutral) search engines.

[5] https://www.genomeweb.com/genetic-research/patientslikeme-builds-multi-omic-longitudinal-program-track-biology-disease-and
[6] https://www.cnil.fr/fr/rgpd-et-donnees-de-sante

Some potential avenues to discuss

It appears important to be vigilant regarding the various sources of information to which people would have access, even if that information is very general or preliminary. Ideally, it may be desirable to encourage patient discernment concerning this type of tool, possibly by supplying checklists and aids for analyzing such “proposals”. Online education/information tools could be proposed, no doubt with two levels: generic for interventional research on a health product in general and, if possible, more specific depending on the disease in question. The expertise of the various Ethics Committees, independent bodies for the ethical validation of clinical research projects, could be mobilized. There may be a need to create bodies to “certify” the information in terms of its form and content and create channels for recourse in the event of dispute.

One point that must be emphasized and that we can envisage is a change in the role of the investigating physician.

As such, the question is: how will participants choose from the protocols and on the basis of what information? As such it is legitimate to consider a review of the conditions of research subjects.

Concerning the choice of protocols (Molecule X from pharmaceutical company A versus Molecule Y from pharmaceutical company B): as mentioned in the introduction, we think that the rule of competition and the model of the patient as consumer/research player will probably prevail.

As such the remuneration[7] of research participants, while authorized in France only for healthy volunteers, could become more or less critical and more or less indirect: in the form of a device, subscription, etc. This funding could be targeted at the patients or patient associations enrolled in a clinical trial. The rules for declaring conflicts of interest that currently apply to investigators must serve as a basis for discussing similar processes for the various players of future trials, including the patient associations.

[7] Not to be confused with potential capped and controlled allowances for the constraints suffered

ENROLLMENT IN THE PROTOCOL

The obtaining of consent and the information process associated with this step are legally supervised specifically (see below), even if these two concepts remain the subject of lively debate given that real and truly well understood information is complex to achieve these days. This step seems to be protected at the present time in France, but the previous step has strong chances of significantly influencing the acceptance process.

The European “clinical trials” regulatory framework is particularly well defined in the text of 2014 (536/2014). Article 29, 2c, concerning informed consent states that the information given to the subject… is provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. A derogation is possible for cluster trials (article 30). This regulation does not address the possibility of online consent and specifies “In accordance with international guidelines, the informed consent of a subject should be in writing.” but the eventuality of another means of collection is envisaged when the participant is unable to write.

The feasibility and acceptability by patients of online consent were tested (6) in the USA from a theoretical point of view and in a study on post-partum depression, a study validated by the ethics committee of the University of California (7). An online questionnaire was linked to the request for consent in order to assess the patients’ comprehension of the process.

SOME POTENTIAL AVENUES FOR REGULATION

The number and type of individuals, groups and institutions involved in clinical research are such that no simple consensual solutions are immediately available. Comparison of viewpoints remains essential in order to bring about a shared diagnosis and to discuss potential regulations for which we can only give a few avenues.

It would be useful for all elements of communication from the sponsor to the potential participants, the content and form of any publicity and information documents not associated with the final consent process be systematically approved by the ethics committees (IRB). This is also anticipated by the European regulation which envisages that patient recruitment procedures be described in detail (Annex I, art 59-60) whether concerning printed materials, audio or video recordings as well as procedures for handling responses to advertisements and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial.

For hypothetical purposes, some procedures could accompany the potential development of this type of practice for which

- in scientific publications, the methods section (description of the study population) would need to describe and quantify the methods of information AND contact.

It may be important to ensure that certain rules governing these trials are not modified, particularly the role of the investigator (and the evaluation of their independence) and the need for a preliminary medical examination.

Conclusion

This new way of organizing research, with preliminary contact of the individuals likely to participate in it has many major and undeniable advantages when it comes to the production of knowledge. However, we are concerned with the ethical points:

What will be the fairness of the information prior to that given when enrollment is proposed?

How can we avoid the exploitation of vulnerable populations (albeit those with access to the information tools)?

How can the public research institutions which are currently generally less well prepared for this technological development withstand competition from the pharmaceutical companies?

Other points can also be discussed. Indeed, it is conceivable for several reasons that the knowledge produced by this type of research is not always optimal, either

- a less “useful” treatment with a better recruitment strategy will get tested at the expense of an alternative, or
- because of the recruitment bias generated by the new medium: patients looking for something new, patients with a keen interest in their health (better compliance, fewer comorbidities, etc.)

At this stage in the enrollment process, we consider it essential and urgent both from a methodological and ethical point of view to continue to educate patients about what research is. Patients must also be able to access information from independent sources before accepting to take part in a protocol. The patient associations play and will continue to play a critical role here, something that the pharmaceutical companies have already understood and taken into account. Finally, the ethics committee members evaluating the protocols must be made aware of these new practices.

1. Wagle N, Painter C, Ilzarbe M, Van Allen E, Frank E, Oh C, et al. Abstract OT2-05-03: The metastatic breast cancer project: A national direct-to-patient research initiative to accelerate genomics research. AACR; 2016.

2. Jones R, Lacroix LJ, Porcher E. Facebook Advertising to Recruit Young, Urban Women into an HIV Prevention Clinical Trial. AIDS and Behavior. 2017;21(11):3141-53.

3. Walters SJ, dos Anjos Henriques-Cadby IB, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ open. 2017;7(3):e015276.

4. Kasenda B, Von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. Jama. 2014;311(10):1045-52.

5. Khozin S, Blumenthal GM, Pazdur R. Real-world Data for Clinical Evidence Generation in Oncology. J Natl Cancer Inst. 2017;109(11).

6. Kim H, Bell E, Kim J, Sitapati A, Ramsdell J, Farcas C, et al. iCONCUR: informed consent for clinical data and bio-sample use for research. Journal of the American Medical Informatics Association. 2016;24(2):380-7.

7. Barrera AZ, Dunn LB, Nichols A, Reardon S, Muñoz RF. Getting It “Right” Ensuring Informed Consent for an Online Clinical Trial. Journal of Empirical Research on Human Research Ethics. 2016;11(4):291-8.