

Stakeholder views on participant selection for first-in-human trials in cancer nanomedicine

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ABSTRACT

Background Participant selection for first-in-human (FIH) trials involves complex decisions. The trial design makes it unlikely that participants will receive clinically relevant therapeutic benefit, but they are likely to experience risks of various magnitudes and types. The aim of the present paper was to describe and discuss the views of investigators and ethics committee members about the choice of trial participants for FIH trials in cancer nanomedicine.

Methods We drew insights from an exploratory qualitative study involving thematic analysis of 46 in-depth interviews with key stakeholders in Europe and North America involved in FIH nanomedicine trials. The present work draws on subset of 21 interviews with investigators and ethics committee members who have either conducted or reviewed a FIH cancer nanomedicine trial or are planning one.

Results Investigators and ethics committee members are aware of the ethics standards for recruiting patients with end-stage cancer into FIH trials, but they nonetheless question the practice and provide reasons against it.

Conclusions Although it is a standard and ethically accepted practice to enrol patients with end-stage cancer and no treatment options into FIH trials of investigational chemotherapeutic molecules, doing so can threaten the validity and generalizability of the trials, thereby weakening translational research. Another possibility is to stratify and include patients with less advanced disease who demonstrate certain biomarkers or cancer genotypes and who have a disease profile similar to that tested in preclinical studies. The latter approach could be a step toward personalized medical research and targeted drug development. Such a patient selection approach requires multi-stakeholder discussion to reach scientific and ethics consensus.

Key Words First-in-human trials, trial participant selection, nanomedicine, qualitative research, empirical ethics

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BACKGROUND

First-in-human (FIH) trials are crucial in translational research for experimental clinical applications, but they also pose the highest level of uncertainty with respect to potential risks to trial participants¹. That uncertainty is attributed to the limited validity and reliability of preclinical research^{2,3}, to questions concerning the appropriateness of animal models⁴, and to the lack of clarity about the mechanism of action of investigational products⁵. The goal of FIH trials is to gather information about the mechanism of action, to study the toxicity and safety profile, and to determine a safe and tolerable dose in humans, which will be the starting dose for further clinical trials in which the

efficiency of the intervention is tested⁶. The dose-escalation design of FIH trials makes it highly unlikely that patients participating in such trials will receive clinically relevant therapeutic benefit, at least in the earliest cohorts testing low doses of the experimental molecules⁷. Trial participants are likely to experience side effects and harms of various types, magnitudes, and probabilities⁸. Some of the harms can be predicted from preclinical animal data. However, data from animal models cannot be reliably extrapolated to human beings, and substantial uncertainty and ignorance persists in assessments of the risks of FIH trials⁹.

Compared with later-stage trials, FIH trials often involve fewer trial participants, thus reducing the number of individuals who could be harmed⁶. But if the participants

selected for such trials are inappropriate, translational research is harmed in two ways: First, individual participants, even though few in number, are harmed. Second, human and financial resources are consumed in conducting trials that do not generate valid, reliable, and generalizable scientific knowledge that can guide further translational research or that necessitate additional preclinical research^{6,10}.

The literature on participant selection for FIH trials mainly discusses 3 different categories of trial participants: healthy volunteers; patients with stable disease on standard therapy, but who suffer nonetheless; and patients with terminal illness who no longer have any standard therapy options¹¹. Researchers working with novel medical technology such as gene transfer and regenerative medicine have pointed out another category of potential FIH trial participants: individuals who are currently asymptomatic carriers of certain genetic or degenerative conditions that will manifest as a disease in future¹².

Participants in FIH trial are vulnerable for various reasons: therapeutic misconception^{13–15}; undue hope and optimism that the investigational product will improve their health, or at least their quality of life¹⁶; perceived pressure to accept what their treating physician feels is good for them; and inadequate appreciation of unlikely benefits but likely harms¹¹. The choice of trial participants for FIH trials involving cutting-edge medical technologies such as gene transfer, regenerative medicine, cell-based interventions, and nanomedicine is further influenced by the novelty of the intervention under investigation, the limited reliability of disease models in animals¹⁷, and the huge hype and hope that such technologies generate in the minds of patients and the general public¹⁸. The hype and hope make trial participants further prone to succumbing to the therapeutic misconception and underestimating the risks and likelihood of harms.

The choice of trial participants for FIH trials involves a delicate balance between the requirements of the study protocol and design (protocol-driven factors) and participant-related factors from the perspective of patients and healthy volunteers. A significant body of literature has explored the motivations, hopes, and expectations of healthy volunteers and patients who participate in various clinical trials, including FIH trials^{19–25}. Patient-related factors influencing the decision about whether to participate in FIH trials include unmet need for treatment options, lived illness experience, suffering and impact on quality of life, willingness to accept higher risks in the hope that the experimental treatment might provide at least symptom relief if not cure, and familiarity with and understanding of clinical trials and investigational molecules.

We believe that the patient perspective on trial participation merits its own investigation. Our research project has two separate arms: one focusing on patient perspectives and the other on expert stakeholders. In the present work, we specifically explore the perspectives of expert stakeholders about the selection of FIH trial participants.

The goal of our paper was to summarize and discuss the views and thought process of principal investigators (PIs) and ethics committee members (ECMs) about the “ideal or most appropriate” trial participants for their FIH trials in nanomedicine. We are aware that FIH trials

constitute a heterogeneous group of trials and encompass a large spectrum of scenarios from FIH testing of a slight modification of an already licensed drug at one end, to the testing of a completely novel investigational molecule based on cutting-edge technology that has never before been tested in humans at the other. For the purpose of the present work, we focused on the latter end of the spectrum, where novel investigational products or molecules are being tested in humans for the very first time, and safety or toxicity data for humans from prior experience with other similar products are unavailable or limited.

We used medical applications of nanotechnology as a prototype for our investigation into the challenges of clinical translation of cutting-edge medical technology. Because of their size or unique physical and chemical properties (or both), nanomedicines allow for the development of highly sensitive and specific diagnostic tools that could facilitate early disease detection and improved monitoring of disease progression. They provide efficient drug delivery mechanisms and platforms, with better targeting to disease lesions and delivery of higher concentrations of drugs at desired sites, thus improving drug efficiency and reducing side effects^{26,27}. Though nanotechnology-based diagnostic and therapeutic interventions are expected to revolutionize the understanding of disease mechanisms and the ability to treat or cure diseases, significant concerns and uncertainties also pertain to the risks and harms caused by nanoparticles to humans and the environment²⁸. That tension between immense hope and hype about the potential of nanotechnology in medicine, and the fear and reluctance attributable to its feared toxicity makes nanotechnology an interesting case study, especially to discuss the challenges it poses in translational research.

Here, we describe and discuss insights from a subset of 21 of 46 in-depth interviews with translational nanomedicine stakeholders based in Europe and North America who have either conducted or evaluated a FIH trial or who are planning one in the near future. Stakeholders discussed mainly nanomedicine-based cancer chemotherapeutic drugs because most of the approved nanomedicines are anticancer agents. Although there is a vast body of literature on participant selection for FIH trials in general and cancer trials in particular, we are not aware of any other empirical investigation in which trial participants for FIH cancer nanomedicine trials have been discussed. We believe that the present work will shed further light on the concerns expressed by scholars working on the ethics of nanomedicine and physicians caring for cancer patients. It will, in particular, help to clarify the reasons and arguments stakeholders use to justify their choice of FIH trial participants.

METHODS

For this exploratory qualitative research, we used in-depth interviews to elicit the views and experiences of stakeholders involved in FIH trials in nanomedicine in Europe and North America. In-depth interviews were facilitated with a semi-structured list of open-ended questions and focused on understanding the various challenges (including ethics challenges) faced by the stakeholders

of translational nanomedicine. Interviews allowed us to build a dialogue with the expert stakeholders and provided them the necessary space to highlight arguments and experiences that they found pertinent and worthy of discussion. All the respondents discussed financial, ethics, patent-related, and regulatory challenges that are applicable to translational research in any cutting-edge medical technology²⁹. But a subset of the respondents who had either conducted or were planning to conduct FIH nanomedicine cancer trials reflected extensively on specific challenges they faced while justifying their preferred choice of trial participants either to themselves or to the ethics committee. The present work focuses on the reflections of those stakeholders and on the specific dilemmas they faced in the choice of trial participants while ensuring scientifically and ethically sound study design and the generalizability of the knowledge gained.

Respondents

We interviewed scientists affiliated with universities, academic centres, small- and medium-size enterprises, and large pharmaceutical companies; physicians and PIs of trials; ECMS or members of institutional review boards; representatives of drug regulatory authorities, patient advocacy groups, clinical research organizations, and venture capitalists. Those roles are not necessarily mutually exclusive. The heterogeneity of the respondents allowed us to understand the challenges of translational nanomedicine from the perspectives of the various stakeholders involved and the specific roles they play in the process, but it also posed a few specific methodology challenges such as theoretical saturation and quantifying responses according to the roles the respondents played. Some of those challenges are described in subsections that follow.

The present work draws on a subset of 21 of the 46 respondents and includes the experiences and opinions of scientists, physicians, PIs (collectively referred to as “investigators”), and ECMS or institutional review board members who had either conducted or evaluated a FIH nanomedicine trial or were planning one in the near future. Their profiles are summarized in Table 1. The remaining 25 respondents did not have specific comments or reflections on choosing trial participants either because they had not considered the topic and were still focused on preclinical research, or their role in translational research did not include having to choose participants for FIH trials.

Interview Guide

An extensive literature review helped us create a list of open-ended questions for the interviews with key stakeholders. This semi-structured interview guide steered the discussion and allowed respondents to describe salient issues, experiences, and thoughts. Stakeholders involved in translational research were expected to have varied professional backgrounds and to play a specific role, hence the interview guide had to be flexible and to address questions relevant to the role the stakeholder played in a particular trial. The guide thus had to be adapted while interviewing an expert in nanotechnology–nanomedicine patent law, who might not have had specific views about participant selection, but who would highlight challenges linked to

TABLE 1 Profile of the expert stakeholders interviewed^a

<i>Affiliation</i>	
Academic researcher	20
Subject matter expert	8
Large pharmaceutical industry	6
Ethics expert or IRB member	6
Drug regulator	2
Venture capitalist	1
Patient advocacy group	1
Industry consultant	2
TOTAL	46
<i>Experience of FIH trials in nanomedicine</i>	
Trial completed	11
Advanced preclinical and planning work	10
TOTAL	21
<i>Targeted disease</i>	
Cancer	9
Diabetes	2
Immunologic	5
Cardiovascular	1
Infectious	4
TOTAL	21
<i>Main drug delivery platform</i>	
Liposomes	8
Gold nanoparticles	3
Silver nanoparticles	1
Polymer micelles	2
SPIONs	2
siRNA	1
Silica multistage vectors	1
Others	3
TOTAL	21

^a Descriptions of the countries in which they work and the roles they perform were intentionally withheld to ensure anonymity. Completed FIH trials in nanomedicine are few in number, and so with the information about the disease target, drug delivery platform, and country, the identity of the respondents could be easily deduced.

IRB = institutional research board; FIH = first-in-humans; SPIONs = superparamagnetic iron oxide nanoparticles; siRNA = small interfering RNA.

patent evaluation and granting, which are linked to the interests of the investors or venture capitalists and hence connected with the ability of an investigator to generate the financial resources to move from preclinical research to early human trials.

The interview guide was pilot-tested with 3 colleagues experienced in qualitative research and the ethics of medical technology. The pilot interviews were excluded from the final data set. The interview guides were approved by the local ethics committee and are published as supplementary material to one of our published articles [<http://www.sciencedirect.com/science/article/pii/S1549963415006218> (subscription required)].

Interviews and Transcription

All stakeholder were interviewed in English by PS between October 2013 and November 2014—in person whenever possible, or over the telephone—using purposive maximum variation sampling¹⁹. Oral informed consent was obtained from all participants before the interview, and permission was asked to record the conversation on an audio device. The ways in which the confidentiality and anonymity of their views would be ensured were explained. Interviewees could refuse to answer any question or could ask for the recording to be stopped for particular sections of the interview. Interview durations ranged between 20 and 60 minutes, with the average time being 50 minutes. Stakeholders continued to be interviewed until data saturation was reached (a stage at which the research team was convinced that no new themes relevant to the aims of the study were emerging with additional interviews)³⁰. Given the heterogeneity of the sample, theoretical saturation was reached at varying time points for the various themes under discussion; timing depended on how many of the stakeholders had views on the particular topic. Together with research assistants, PS transcribed all interviews verbatim and in full; PS also checked all interviews against the audio recording and sent the transcripts to respondents to check the contents and the accuracy of technical details, as well as to solicit additional thoughts or suggestions.

Data Analysis

At the beginning of data collection, PS simultaneously undertook a preliminary data analysis, the insights from which were included in subsequent interviews. She used the qualitative analysis software MAXQDA (Verbi GmbH, Berlin, Germany) to carry out deductive data coding. DMS undertook a similar exercise manually. The resulting codes were built into themes and discussed using manual and software-assisted data analysis until the research team reached agreement.

The research team extensively discussed the advantages and disadvantages of deductive and inductive data coding as an approach for the data analysis, eventually agreeing on deductive data coding in light of time and funding constraints. For the present work, the goal was to discuss the range of views and experiences rather than the frequency of similar views. So, instead of the results being quantified, they are described in general terms: for example, “a few,” “some,” “many,” “all.”

Ethics Approval

The ethics commission of northwest and central Switzerland (Ethikkommission Nordwest und Zentralschweiz) approved the research project and the interview guide in January 2013.

RESULTS

Of 46 respondents, 25 were working on various stages and aspects of clinical translation in nanomedicine such as bench research, animal experiments, toxicity assessment, and manufacturing of the required investigational compound under the conditions of good manufacturing practice; the remaining 21 had direct involvement with FIH

trials in various capacities (investigator, trial physician, trial coordinator, ECM, representative of a drug regulatory authority). The FIH trials were focused on nanotechnology-based drug delivery platforms in cancer, diabetes, immunologic disorders, cardiovascular diseases, and infectious diseases.

With those 21 stakeholders, we explored views about the “ideal or most appropriate” trial participant for their FIH trial in nanomedicine and the underlying reasons for their choice. All 21 stakeholders advocated for a case-by-case assessment of participant selection for FIH trials of various interventions or experimental molecules and referred to various ethics guidelines such as the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>), regulatory guidelines for the investigation of new drugs from the U.S. Food and Drug Administration (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm>) and the European Medicines Agency (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000564.jsp&mid=WC0b01ac05806403e0), and clinical research guidelines such as the *Guideline for Good Clinical Practice* from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf), which provide guidance on participant selection and clear formulas for calculation of the starting dose for FIH trials.

Because most nanomedicines have been developed and approved for cancer treatment, the focus of the discussions was on nanomedicine-based cancer trials, but respondents also mentioned other trials involving stem-cell therapy and gene transfer when making their arguments. We describe our results using select quotations from the subset of 21 interviews to highlight most important aspects of the theme under discussion. Our aim was to demonstrate the spectrum of arguments rather than to quantify how often a particular argument was used. To protect the confidentiality and anonymity of respondents (Table 1), we tag each quotation with a respondent number (R1, R2, ...), followed by their role.

“Ideal” Participants Might Not Always Be the Most Ethical Choice

All stakeholders were aware that most FIH cancer trials include patients with no treatment options, per the international ethics standards.

You will never, *never* accept a study that is a healthy volunteer study with a chemotherapeutic agent. You test it in tumours, immunocompromised mice with tumours, then in patients who are extremely sick with metastasis, tumours which cannot be cured by any other existing drug. You try it first on such patients and then you slowly go backwards to less sick patients.

— R6, ECM

We ideally would have a patient who is partially previously treated, because that is also logical. It is also ethical that you should first give the patient

a well-known treatment—the standard of care so to say—and if the first and the second line is not working anymore, only at that point, is it ethical to go on continuing with something novel, either for the sake of science or for it might really have an added value in that specific patient.

— R21, scientist planning a FIH nanomedicine trial

Some stakeholders highlighted the constraints and challenges of including only the sickest patients in FIH trials.

[They have had] a lot of other treatments before. They often are not in a good condition. They have very limited life expectancy. These are patients who always have problems—lot of the adverse events and serious adverse events. These are not randomized controlled trials, so many of these adverse events are attributed to the disease itself and not to the drug. So this is not the best way. But when a patient has treatment options with proven benefit, it is not ethical to use a drug where you don't know first the dose, the efficacy, and it is debatable if patient will have any benefit. This is why most of the new drugs in oncology are tested on dying patients. It is not ideal for the drug, but it is not ethical to give patients a treatment which might be inferior to an existing treatment.

— R12, physician and PI who conducted a FIH nanomedicine trial

Other stakeholders argued that the ideal participants are actually newly diagnosed cancer patients, or even better, patients with specific mutations or those who are known to have particular biomarkers that can be detected using imaging techniques.

Ideal patients are the new patients that get diagnosed with the tumour because they have no prior treatment and no resistance. Those will not be allowed to join such trials of course. You have to do your trials in terminal-stage cancer patients, after which you can decide that it is safe enough to apply this technology and then you need to find a certain group of patients that will participate in the phase II trials when the efficacy will be studied. Even at that stage, you won't get new patients but pre-treated patients. But there you can try to get some cure. It is logical especially in phase I trials where we only focus on the risks and toxicity, tolerable dose, etc. But in the next phases, you would like to treat the right patients that could benefit from this particular application.

— R8, scientist planning a FIH nanomedicine trial

Bear in mind that we have stage IV patients with metastasis all over. So anyway it will be palliative treatment that they will take. In that context, sometimes we can have a strong rationale that these patients might benefit from this new drug. Let's say we have patient with stage IV lung cancer

with a particular molecular marker. So if we know that these patients do not respond to any other treatment, and that we have found in pre-clinical study that, in cell model and in animal models, tumours with these specific mutations respond to the treatment that we want to test, we have a rationale that may be strong enough to go in naïve patients [treatment-naïve patients whose cancers have been diagnosed late].

— R23, trial coordinator from a large pharmaceutical company

Choosing treatment-naïve, recently diagnosed cancer patients for FIH trials was perceived as ethically challenging by all stakeholders, but they also pointed out the importance of other factors such as type of cancer, availability of standard therapy, prognosis, and time available to intervene.

We often discuss whether the knowledge you want to gain requires a study in patients with end-stage disease or [whether] you can test it on patients who are not that sick. It is a very difficult decision. What you don't want is to give false hope to patients with end-stage disease. You can also do part of the study in newly diagnosed patients or patients in between on the spectrum of disease progression, depending on life expectancy of the patient with his or her particular type of cancer. If we use newly diagnosed patients to study toxicity, one must assess if they have a possibility of trying other existing established therapies three or four weeks later or they have to start immediately with the accepted standard therapy. If we know that the experimental therapy under investigation is not going to negatively influence the standard established therapy after a few weeks—there is no cross-reaction, or resistance, and we can have that time gap—it can be a good case.

— R9, ECM

Another argument for testing new drugs in relatively healthier cancer patients is to better assess side effects and toxicity.

In the first- or second-line treatments, it depends on the disease but when the patient is still fit and still has higher chance to benefit from the drug. On every drug, there is a ratio between the efficacy and side effects. And if you go to the patients who are in worse physical condition, the side effects will be more pronounced than the efficacy. This will not be the case if the patients are fitter and if you treat the patients during the first or second line.

— R12, physician and PI who conducted a FIH nanomedicine trial

Stakeholders also noted the specific character of particular cancers: some have very rapid progression and do not have many treatment options in the first place.

It depends on the disease, actually. For example, non-small-cell lung cancers, it is matter of debate. We know that non-small-cell lung cancer is a disease with rapid progress, and patients deteriorate quite quickly and only about sixty per cent to seventy per cent of all patients receiving first-line therapy get the second-line therapy. This will also be the case if you treat these patients in FIH trial with a new drug. And there will be one third or more of these patients not receiving the established first-line therapy. If you have a disease where most of the patients are dead after twelve months, this is quite different from a disease where you have time. For example, low-malignant lymphoma when you have time in years. It might be the case here to test the new drug in first line, so you can rescue them in the second line with an established treatment.

— R31, PI planning a FIH nanomedicine trial

First-in-human trials are typically toxicity- and dose-finding studies. Another factor that influences participant selection for FIH trials is the burden of risk for participants and, particularly, how long they might have to live with those risks.

Well, “ideal” is a difficult term in this context because what they usually want for these trials are patients who will not be bothered by the long-term risks because they will not survive long. So if you want to know the ideal oncology patients to participate in this kind of trials, it is the patient who is certain that there is no treatment anymore but who is in a reasonably good condition. You don’t want to burden someone who is really at the end of his life and in a bad health condition.

— R22, physician and ECM

Challenging the Standard Design of FIH Trials

Some of our respondents criticized the traditional dose-escalation model of FIH trials, arguing that it might not be the best model for trials involving novel medical technology such as nanomedicine, stem-cell interventions, or gene transfer. One of the reasons for that stance was a lack of clarity concerning the dose–response relationship. Another concern was whether it was ethical to use the standard starting dose calculation from the animal models (as elaborated next, in discussing the case of stem-cell injection into a spinal cord lesion).

But the problem is [pause] to do a FIH study with ineffective dosage which provides him absolutely no benefit and makes him more desperate. One actual example is the vaccination against the Ebola virus. I don’t think they did a classical first-in-man study; they probably started with the expected immunogenic dose and looked if it works, if antibodies are generated. They don’t challenge them with a dose which is one hundred times smaller than what you would expect to make an immune reaction. The classical first-in-man study

is excellent with new drugs, but in these situations like the spinal cord lesion it is not feasible unless you believe that even a very small amount of these stem cells can create a malignant tumour.

— R46 physician and ECM

DISCUSSION AND CONCLUSIONS

The goal of FIH trials is to produce valid, reliable, and generalizable scientific knowledge that could guide further translational research¹⁰. Ethics evaluations of such trials often hinge on balancing harms to the trial participants against the social and scientific value of research, rather than on a traditional risk–benefit evaluation for the trial participants³¹. Scholarly discussion about involving patients with end-stage disease and no proven treatment options in FIH trials has focused on the vulnerability of those patients, the high likelihood of therapeutic misconception, the problems of information disclosure, and participation in decision-making¹¹.

Our results, however, highlight a significant conflict experienced by investigators and ECMs between doing what good ethics practice mandates (that is, enrolling only patients with end-stage disease and no treatment options into FIH trials, thus protecting other patients against unjustified and uncertain harms of exposure to unproven interventions) and what good scientific practice requires (that is, selecting less-ill patients for such trials so that results could guide further translational research). Abiding by ethics norms in terms of acceptable risk–benefit assessment for individual patients in turn adversely affects the clinical trial’s validity and reliability. Patients with advanced disease and no treatment options are fragile and weak. Enrolling them into FIH trials to assess an investigational product’s safety and toxicity profile increases their risk of experiencing severe side effects and adverse reactions. Because most FIH studies are not randomized controlled trials and do not involve blinding, many of the adverse events patients experience in such trials might not be accurately attributed to the investigational drug but instead to the underlying disease. That possibility will significantly weaken the goal of gaining scientific knowledge, either necessitating further preclinical testing or guiding later clinical research and thereby potentially harming more patients who will be eventually tested with the same product in phase II/III trials.

Some researchers have argued for a modification of dose-escalation FIH trials, such that most trial participants will receive a potentially effective dose¹¹. That change will be beneficial only if the investigational product indeed turns out to be efficacious—a finding that is not often the case in many FIH trials. Large numbers of investigational products fail to demonstrate efficacy in humans, the requirement for a product license³². If the investigational product has serious side effects, then the trial participants in any such modified FIH trials are also likely to experience more serious side effects proportional to the higher dose received, and thus more patients than necessary will be exposed to the harms.

Others have argued for more rigorous preclinical research using appropriate animal models, and bringing

randomization and blinding into preclinical animal experiments to achieve higher methodologic and scientific rigour such that potential harms in humans can be better predicted¹⁰.

Are there ways to move trial designs in terms of patient recruitment from terminally ill patients to other patients whose disease is not so advanced? That latter group of patients could be included in FIH trials with new drugs for a short period of time and could later be rescued by proven standard therapy provided there is no drug interaction or resistance related to their trial participation.

Given improved understanding and assessment of biomarkers and cancer genotyping, as well as advances in imaging techniques, it will be worthwhile to stratify patients further, thus choosing for particular FIH trial only those who express a certain biomarker or who demonstrate conditions similar to those tested in preclinical animal models, regardless of how severe their disease is at the time of trial participation. Patient recruitment of that type could be a step toward personalized clinical research in a limited sense. In cancer chemotherapy using liposomes as a nanomedicine drug delivery platform, for example, it might be possible to preselect patients who demonstrate enhanced permeation and retention of liposomal nanoparticles on imaging studies. Many liposomal chemotherapeutic formulations use the enhanced permeation and retention effect as the main passive mechanism of drug delivery to cancerous lesions³³. The nanoscale size of liposomes filled with active licensed chemotherapeutic drugs allows for their extravasation from leaky tumour vasculature into the tissue spaces and tumour stroma. The active chemotherapeutic compound encased within is then released, thus concentrating the drug locally, improving the efficacy of cellular lysis and minimizing toxicity to surrounding healthy tissue. Not all patients have tumour vasculature that is leaky enough to allow for the distribution of a sufficient concentration of liposomes into the tumours, but patients who have sufficiently leaky tumour vasculature can be identified using certain imaging techniques. Although that approach will involve more costs because of the inclusion of diagnostic and prognostic imaging endpoints in such FIH trials, researchers will be able to choose appropriate trial participants in whom the drug can be concentrated locally and to produce a reliable scientific understanding of the mechanism of action and toxicity of the investigational product and a preliminary assessment of efficacy, if any. Furthermore, other patients (with no demonstrated enhanced permeation and retention effect) who are unlikely to benefit from the liposomal investigational product will be protected against unnecessary harms related to their trial participation by exclusion at the outset of the trial.

Finally, a discussion about appropriate participant selection is incomplete without meaningful engagement with patient populations or patient advocates in trial planning, evaluation, and decision-making. The framework for such engagement has to be flexible, proportionate in terms of risks and benefits, and transparent. However, it is not always easy to define who the appropriate representatives of patient populations are³⁴ and whether they could objectively assess potential harms and benefits for each

trial. The literature describes the role of patient advocates in advocacy for fund mobilization, communication with potential trial participants, support for newly diagnosed patients, and informing policy and oversight^{35,36}, and yet it is debatable what role—if any—they should play in ethics evaluations of FIH trials of cutting-edge medical technologies. Our research project focused on professional stakeholders and did not receive input from patients, with the exception of 1 representative from a patient advocacy group. Further research into understanding what meaningful patient engagement could contribute to translational research will be immensely valuable.

We are aware of a few methodology limitations related to the purposive sampling technique in the present study. Although the results of this exploratory study have limited generalizability, they raise important questions about appropriate trial participants for FIH trials in cancer nanomedicine, thus generating an important debate. In-depth interviews also allowed us to gain insight into the reasons for the feeling on the part of key stakeholders of FIH nanomedicine trials that patients with advanced disease might not be the appropriate participants in early translational research in humans, even though such participants are justified and recommended by ethics guidelines. Further studies with larger and homogeneous study populations will increase the evidence base and help to determine whether these dilemmas about participant selection in FIH cancer nanomedicine trials are also relevant to any FIH trials with cancer patients regardless of whether they involve cutting-edge medical technology.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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