

Insufficient recruitment and premature discontinuation of clinical trials in Switzerland: qualitative study with trialists and other stakeholders

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Summary

AIMS OF THE STUDY: Premature discontinuation occurs in about 25% of randomised clinical trials in Switzerland; it mainly affects investigator-initiated trials and is mostly due to problems with recruitment of patients. The aim of this study was to qualitatively investigate reasons for trial discontinuation due to poor patient recruitment and suggestions to address those reasons in the Swiss context.

METHODS: We conducted semi-structured interviews with trialists whose trials were discontinued because of recruitment problems, other experienced trialists, and stakeholders in clinical research in Switzerland. Interviews were audio-recorded, transcribed verbatim, and anonymised. We analysed the transcripts using deductive coding and built up themes that were continuously discussed within the research team.

RESULTS: Of 65 invited Swiss trialists and stakeholders, 39 (60%) agreed to be interviewed and contributed to this analysis. We identified four main themes of reasons for poor recruitment: (1) Switzerland has a decentralised healthcare system with many small hospitals and few patients per hospital, many research regulations, no standardisation of medical records across hospitals, and a heterogeneous ethics assessment of study protocols. There is little collaboration of different stakeholders in clinical research and a lack of prioritisation of projects. (2) Limited human and financial resources, especially in the academic setting, compromise research questions and size of clinical trials. When funding is used up this typically triggers discontinuation of already delayed clinical trials. (3) Investigators face underdeveloped research networks and a limited collaborative attitude among clinical researchers. They typically embark on clinical studies with a great deal of optimism but insufficient preparation. (4) Swiss patients have universal health coverage and many treatment op-

tions. Negative media coverage of clinical research and a lack of accessible information for patients about ongoing clinical studies frequently make participation in clinical trials less attractive. More interactive structures and collaboration across stakeholders were mentioned as potential solutions to tackle the problems.

CONCLUSIONS: Recruitment of participants into clinical trials in Switzerland is challenging because of various, often interlinked factors related to the Swiss health system, available funding, investigators, and patients. Common goals and concerted efforts by involved stakeholders appear necessary to achieve improvement.

Key words: randomised controlled trials, early termination of clinical trials, poor recruitment, stakeholder interviews

Introduction

One out of four randomised clinical trials (RCTs) in Switzerland is prematurely discontinued. This is problematic because study participants may have been exposed to potential health risks and other burdens of participating in a trial that was discontinued without the research question being answered [1]. In addition, scarce research resources are wasted if RCTs are not completed, and evidence that may still contribute to systematic reviews and meta-analyses, as well as the root causes behind the discontinuation, are not published.

In Switzerland, Germany and Canada, the most common reason for RCT discontinuation is insufficient recruitment of trial participants, particularly in investigator-initiated RCTs [1]. Various qualitative and quantitative studies have already suggested different barriers to and facilitators of recruitment [2–11]. Most of these studies, however, focused on specific disciplines or countries other than Switzerland. In order to find suitable lever points, it is important to understand the mechanisms and root causes underlying insufficient recruitment to RCTs and to capture

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the views of the full spectrum of involved stakeholders in the Swiss clinical research arena such as individual investigators, research networks like the Swiss Group for Clinical Cancer Research (SAKK), the Swiss National Science Foundation (SNSF), research ethics committees, the clinical trial units (CTUs) federated within the Swiss Clinical Trial Organisation (SCTO), swissmedic, the pharmaceutical industry and contract research organizations, patient representatives, and the Federal Office of Public Health (FOPH).

The present qualitative research was built on the findings of a retrospective cohort of RCT protocols [1] and a systematic review that suggested that a large majority of reasons for poor recruitment in RCTs is preventable if thorough feasibility assessment and pilot studies are undertaken in advance [12]. The aim of this paper is to elucidate reasons for trial discontinuation due to poor participant recruitment and to discuss solutions specifically in the Swiss context.

Materials and methods

No ethics approval was necessary according to the Research Ethics Committee of Northwestern and Central Switzerland (EKNZ UBE-15/50). This interview study was considered unproblematic from an ethical point of view.

Of 65 invited Swiss trialists and stakeholders, 39 (60%) agreed to be interviewed and contributed to this exploration of reasons for poor recruitment to clinical trials in Switzerland and ways to prevent it.

Study instrument

We developed a list of open-ended questions to facilitate in-depth interviews with the respondents. These questions helped to steer the discussion while providing respondents with sufficient freedom to describe experiences and perspectives that they deemed relevant to our research questions. We finalised the interview guides with the inputs from two pilot interviews and feedback from other qualitative researchers (see appendix 1 for details of interview guides).

Interviews and transcription

We identified the respondents through our professional networks and the list of principal investigators whose trials were discontinued in the past because of poor recruitment [1]. Between August 2015 and November 2016, MB and PS conducted all interviews in English, in person whenever possible or by telephone at times convenient to the respondents. We continued recruitment till theoretical saturation was reached. The latter is defined as the moment in qualitative research when researchers are convinced that additional interviews do not generate new themes related to the research question [13]. We ensured confidentiality and anonymity of each respondent by removing all personal identifiers such as their names, affiliations or professional titles. We retained generic details such as the role of the respondent as the member (including presidents) of a research ethics committee or representative of a large pharmaceutical company for the purpose of analysis but took utmost care not to disclose respondents' identity. Before each interview, we obtained oral informed consent and the per-

mission to record the interview on an audio device. The average duration of interviews was 35 minutes; the range was between 10 and 60 minutes. We anonymised all interviews at the level of transcription and saved each transcript with a consecutive number such as T1, T2... for the trialists whose trials were discontinued because of recruitment problems, and R1, R2... for other respondents. Three research associates who had signed the confidentiality agreement transcribed each interview verbatim. PS verified each transcript against the audio recording and resolved any disparities or queries. We gave the respondents an opportunity to review their interview transcript but all except two decided against it. These two respondents added more details to their original statements to improve the clarity but did not remove any details.

Data analysis

PS and MB read the interview transcripts multiple times to get a thorough understanding of the data. PS coded all interviews using the analysis software MAXQDA version 12 and MB did the same manually. We carried out deductive coding guided by our main research question, which was then built into thematic analysis [14]. The smallest units of analysis were sub-codes, which were built into codes. Codes were further merged with other related codes to build themes. The codes and themes were continually discussed within the research team to ensure agreement on the iterative process of qualitative data analysis and to minimise bias due to subjective interpretation.

Results

After describing the characteristics of the respondents we elaborate on four main themes with regard to reasons for poor recruitment that are related to funding, health systems, investigators, and participants. We simultaneously discuss ways in which these reasons could be addressed drawing on suggestions from our respondents and proposing several own ideas. We use select quotations from the data to elaborate on these points. Our focus is not on how many respondents stated the same reason or proposed the same solution but to describe a spectrum of ideas obtained through interviews and to facilitate discussion.

Profile of respondents

We interviewed a total of 12 academic clinicians with extensive experience of conducting clinical trials as principal investigators or co-principal investigators. Six of these trialists discussed specific details of their "failed" trials discontinued because of poor recruitment. Five out of these six discontinued trials were investigator initiated and funded through SNSF, SAKK, professional organisations or a department's own research budget, whereas one trial was industry sponsored. They included RCTs in the fields of urology, diabetology, obstetrics, cardiac anaesthesiology, pharmaceutical sciences and transplantation medicine. The expected sample size for these six studies ranged between 70 and 300 but the actual sample of respondents included ranged from 20 to 140 when the trial was discontinued. All respondents reflected on reasons for discontinuation of clinical trials irrespective of the type of intervention (pharmaceutical product or medical device), the phase of the clinical trials and the funding source for the study. How-

ever, the focus of their reflections was on the comparison between investigator-initiated trials and large pharmaceutical industry-sponsored trials, which differ significantly in terms of the research questions under investigation, planned sample size, risk-benefit ratio for participants, expected outcome or the goal for conducting trial (obtaining licensing approval from local or regional drug regulatory authorities vs academic career step) and infrastructure and human resource available for conducting the study.

In addition, we conducted interviews with six representatives of the university hospital based Swiss CTUs, three members/presidents of ethics committees, ten representatives from pharmaceutical companies with long experience in planning and implementing large industry-sponsored clinical trials, two spokespersons from Swiss and European Union (EU)-based patient organisations, two representatives from the SNSF and the FOPH, and a representative each from the SAKK and swissmedic. This heterogeneous group had experience of working in clinical research in Switzerland, as well as in-depth understanding of the global clinical research environment. This allowed them to reflect on differences and similarities of conducting clinical trials in Switzerland as compared to the United States or the EU. Many of these respondents had multiple perspectives depending on their current or former professional role. For example, all three members/presidents of ethics committees had conducted clinical trials themselves in the past. Further, some of the industry representatives had been academic investigators in their early professional life and thus could retrospectively reflect on challenges of conducting investigator-initiated trials in comparison to their current role in planning and monitoring large multi-centre industry-sponsored RCTs. We believe this diversity of perspectives helped us understand certain details and nuances of conducting clinical trials in Switzerland.

Theme 1: Factors related to funding available for clinical research

The most recurrent theme in discussion was challenges related to funding available for investigator-initiated trials as compared to industry-sponsored trials. Our respondents repeatedly stated that acquiring sufficient human and financial resources for the entire duration of an RCT is the biggest challenge for investigator-initiated trials. All respondents were aware of the various funding schemes of the SNSF and appreciated those possibilities. However, they also expressed their concerns that clinical research requires high professional standards which are quite challenging to achieve and sustain in academic settings unless significant and continuous efforts are put into building a professional workforce dedicated to clinical research through education and training. Building such a workforce takes decades of careful planning and systematic implementation, and needs to be addressed at the system level. It requires building strong research infrastructure in university hospitals, where clinical research should not be something that one carries out in addition to patient care but is rather deeply integrated with it. The resources needed for building such academic research centres and institutions with an international reputation for high quality research goes beyond the funding received by individual investigators to conduct a specific trial and yet is crucial to encourage patients to participate in clinical research. They

further argued that training of research staff alone is not sufficient, but systems must be in place to retain trained researchers within academic settings by creating career opportunities and other incentives. Frequent turnover of clinical trial staff in academic settings was mentioned as one cause of a lower standard of clinical trial implementation. The other parameter which links with availability of funding is the time clinicians can dedicate to their research-related activities. This is where human and financial resource planning come into play as described below.

“...I think at the present time, research projects in academic settings are not given enough priority and also devoted time. I very often see studies, protocols which we receive, where we can guess that the clinician will not have time to run this project by himself. There is no local funding. They do that on – I don't know in the 25th hour of the day. There is no real help in infrastructure. And of course this has an impact on recruitment, I guess. If you have a well-organized consultation, then patients are identified, let's say, by a good and systematic way and so you don't lose those patients. I think that can help.” (R28 Ethics committee member)

Seven respondents highlighted the strategic importance of trained and experienced study nurses and, in the context of obstetrics, midwives, and commented on their rather limited involvement in the Swiss context as quoted below.

“What I don't see enough used in Switzerland as a tool are study or trial-nurses. I think that is a wonderful tool to get better access to the patients and to keep them happier once recruited for the simple reason that they have more time and they don't have these hierarchical barriers when talking to the patients.” (R24 Representative of patient organization)

Investigator-initiated RCTs often start out with optimism but soon face practical challenges in recruitment. This could be to the result of a number of factors, such as inadequate funding at the beginning of study (Swiss trialists R3 and R21), limited or no funding for the planning phase or to undertake rigorous feasibility assessment (Swiss trialist R16), inability of the principal investigator to procure additional funding during the course of ongoing trial (Swiss trialist T13) and errors in judgement by the principal investigators while planning the budget of the study (Swiss CTU representative R1 and the trialists R8 and R11). The most common reasons for a slower than expected rate of recruitment were extremely rigid and narrow eligibility criteria, ineffective screening of all potential patients to assess their eligibility to be part of clinical trial, eligible patients refusing to participate because of the increased burden associated with the study or the lack of any direct benefit. Without systematic screening of each eligible patient by a study nurse or other physician colleagues, often the task of recruitment falls on the principal investigator alone or is delegated to time-constrained assistant doctors. As a consequence, recruitment frequently takes longer than expected, yet available funds are being used as planned. If a principal investigator is unable to procure additional funding for the same research, they eventually must stop the trial. A few respondents pointed out that increasing funding alone will not change the situation and it should be coupled with better assessment of protocols by funding bodies. This would require funding bodies to recruit reviewers who are up-to-date with current clinical research methodology, together

with the senior academics who contribute their time and experience.

“I would very much welcome that in the Swiss National Science Foundation, there would be more people who understand clinical research. And not only purely medical ones but health system research, and also the newer methodologies, implementation science, which is I think absolutely the future – very difficult but with much more potential than just an RCT.” (T12 Swiss trialist sharing experience of specific discontinued trial)

One of the respondents sharply stated that studies without proof of feasibility and a clear plan of recruitment based on patient data should not be funded by any funding agency to ensure fair utilisation of available resources (R10 CTU representative). Another respondent insisted that funding bodies such as SNSF or SAKK should mandate rigorous feasibility data, as required by the pharmaceutical industry (T13 Swiss trialist sharing experience of specific discontinued trial). But it was also noted that significant time, money and manpower is needed to monitor trial implementation at sites where an industry sponsor is not involved. One respondent questioned the logic of initiating a large number of trials in Switzerland that are not feasible owing to low patient numbers and may not even have direct relevance to the Swiss population. His argument was based on better utilisation of available resources as described below. *“I also think – and that’s a very elitist (laughs) opinion, that probably one should limit the number of clinical trials that run in Switzerland. Switzerland is a small country and we should focus on few really good trials. The numbers of clinical trials have increased dramatically, we don’t have more patients and we do have a bit more resources but not in the same relation as the increase in trials. So I think to achieve this, there should be more networking or more connections between the large money givers for academic trials, so that they really discuss together which are the important trials. And not someone supports part of one trial and the other agency supports some part of another trial. So 10 trials are partly funded but not one big trial where really everyone is behind it. It is always difficult to decide who should have the leading role in this. And in my opinion this should be the SNSF. But it is not working at the moment of course. And there are many people who don’t think this is the right thing to do.” (R20 Swiss trialist)*

Theme 2: Healthcare system related factors

Switzerland with its decentralised healthcare system, specific regulatory requirements and comparatively small numbers of patients per hospital faces unique challenges in large international multicentre trials as described below.

“When it comes to big phase III trials, we are not competitive at all. Because there they want to have a high input of patients and there we are very handicapped for many reasons. First, we have small hospitals. Even our big hospitals are small hospitals. Zurich hospital is a small hospital compared to a hospital in Berlin or Vienna or Paris or London. So we are not very competitive in terms of numbers of patients and type of patients. Then the second burden is that Switzerland is very expensive. When we do multicentre studies at the amount they pay in Europe, we can never pay our – the cost of a patient in Switzerland because, it’s almost half of the price in any other countries! So they have to adapt for Switzerland the price. They don’t

like to do that. And then because it’s a small recruitment or slow recruitment in Switzerland, they always start implementing the studies in large countries like Poland, Germany, France, Spain, Great Britain, Italy and come at the last minute to Switzerland, to get 20–25 patients. We are really a bit slow, we have few patients and we come late in the introduction in the study. (T4 Swiss trialist sharing experience of specific discontinued trial)

Rather complex regulatory and ethics approval procedures in Switzerland further slow down the agreement between the sponsor of the trial and the local site, thus delaying recruitment.

“...the second reason is we are highly regulated. So in other words, for any sponsor or even if you do investigator initiated studies, to implement studies is exceedingly difficult as compared to others. The third one is the regulatory aspects through Swissmedic which is different from other European countries, is also an impediment. So there are several hurdles which make it not so easy in Switzerland to enrol patients into clinical trials or to be even considered for international clinical trials. Why do we need ethics committee approval in Bern, Zurich, Lausanne, Geneva? Is ethics different in these cities? I would go even broader, is it different in Europe or Western Europe? I mean, basically it doesn’t make sense. If you have a multicentre protocol which may even have FDA oversight, then you have specific details from the ethics committee in Bern. It just does not make sense. It just costs time and impairs the recruitment because we are frequently not considered anymore, particularly because of the stringent oversight from the Swiss ethics committees. I really think a major limitation in Switzerland is the overregulation through the ethics committees and Swissmedic and that one needs to have a broader Pan-European perspective on the issue.” (R21 Swiss Trialist)

All respondents acknowledged and appreciated the role of CTUs to standardise clinical trials in Switzerland, but a few respondents challenged the idea that every trial must be reviewed and approved by a CTU and raised concerns about affordability of CTU services. In general, CTUs were seen as guides and technical experts who helped investigators write realistic protocols. Many respondents, including representatives of large pharmaceutical companies, suggested that a database or a track record of all sites involved in clinical trials in Switzerland, grouped by disease areas and special interests, would be highly valuable. Such a database could help researchers who are interested in a particular disease to get in touch with other researchers working in that domain and also help industry sponsors to identify sites with proven track record. All respondents agreed that developing research networks is the best way to strengthen clinical research in Switzerland. They often described their positive experiences of doing research with the SAKK or SwissPedNet but at the same time accepted that development of effective research networks is a time and labour intensive process and requires sustained motivation and leadership.

The potential of smaller regional hospitals and clinics as trial sites was highly debated. Some researchers felt that these hospitals do not have the necessary administrative infrastructure or trained manpower and often do not recruit a single patient whereas creating networks with other university hospitals is easier and more successful. But there

were also opposing views advocating inclusion of smaller hospitals in clinical trials as demonstrated below.

“... another access could be to involve regional hospitals more depending on the type of research questions. Often the doctors at regional hospitals, so non-university hospitals, will be quite happy to collaborate in research; they are just not in this milieu anymore and maybe they wish they could. They are maybe a little bit forgotten or people don't think about their potential necessarily. So I am not only thinking that collaborations should be between the university hospitals, but also if there was a kind of networking mechanism, a way of signalling your interest in xyz, that would then be visible and you could in this way get involved in collaborative research if you are at a local hospital. That may help too.” (R25 CTU representative)

Some of our respondents were concerned that many private clinics and smaller hospitals in Switzerland are reluctant to refer their patients who might be eligible for clinical trials to trial sites (often large university hospitals and cantonal hospitals) due to fear of losing a patient and the money thereby. Two factors that need to be addressed here are (1) ways to inform the clinicians in peripheral hospitals regarding ongoing trials and (2) to have agreements that the patients will return to the referring hospital once their participation in the trial is over. An up-to-date, easy-to-search database of all registered and ongoing clinical trials could address the first challenge provided that clinicians are sensitised to regularly check such a database. The second challenge needs further scrutiny and discussion as it depends on the patient's choice and the arrangement with the health insurance company.

Finally all respondents highlighted the importance of standardised medical records across Switzerland. Many of our respondents felt that the recent development of a personalised health network in Switzerland could facilitate creation of a nationwide patient database, not just for rare diseases but rather a unified system of electronic medical records that are standardised nationally, accessible electronically and hence critical for feasibility assessment of RCTs.

“The fact that there is not a unique identifier, number for identification with exception of the AHV number in Switzerland, is a limitation to communication between systems, between IT infrastructures. So that's a point that is a limitation, I would say, for multi-centric clinical research. It's a detail but I think there is an impact since clinical database has an easy way to communicate, to screen people and so on... Then at the institution level which is a lower level but closer to the patients, I think a better integration of clinical research structures, once again homogenizing standard operating procedure, a type of software, maybe sharing resources including human resources dedicated to clinical research. I think integrating progressively the different clinical research structures that are existing in one institution is of importance.” (R19 CTU representative)

Respondents of this study also discussed the importance of trial registration and the creation of a comprehensive database of ongoing trials accessible to all interested stakeholders.

“Well firstly, I think that a national clinical trials registry would help. A portal, where patients and doctors can find and register to clinical trials, which is accessible, meaning

that it is on several different websites, like patient organization-websites, hospital-websites and different websites to reach patients. And there could be done a lot more by public institutions to raise awareness about clinical research in Switzerland, and why it is important to participate in such trials, not only for the society, but also for individual patients, so that they may get the best treatment if they participate in trials. Often people don't have this information.” (R27 Representative FOPH)

One of the respondents who worked in The Netherlands before moving to Switzerland was rather shocked to realise that not all trials in Switzerland are registered. The respondent argued that the trial registration and providing feedback on the progress of the trial to relevant authorities on a regular basis is the responsibility and accountability of each principal investigator and should be taken seriously.

“I think the hospital or the academic institution should know about their own trials. I think that's the minimum! I mean basically I would even think that if ever an audit looks into the competence of such a centre that they should look into them. I mean imagine in the extreme case you have a unit in a hospital which is not able to complete 50% of their trials, right? And I think that's a serious quality issue! So if you get an audit then that means it needs to be transparent. When there is something wrong with the quality of the investigators or with the structures or with something. I mean basically it's the competence of the centre when they cannot complete their trials.” (R31 Representative of pharmaceutical industry)

Theme 3: Investigator-related factors

Pertinent themes included challenges in developing collaborations with other Swiss hospitals and the way in which success of clinicians is measured. These two factors are linked in a number of ways. Given the small population, high density of hospitals and smaller number of patients per disease condition, it is critical that Swiss hospitals create effective collaborations, research networks and efficient referral systems for patients to the recruiting sites. The general experience of the respondents was quite the opposite, even though they all admitted that things are improving. Three out of six trialists whose trials were discontinued because of poor recruitment had faced serious challenges in establishing meaningful and functional collaborations with other hospitals or colleagues from different disciplines from the same hospital as described below. *“Sometimes you have the feeling it's easier to cooperate with colleagues from the United States than with colleagues here in Switzerland. There is still not an extremely cooperative feeling between some of the players here.” (T5 Swiss trialist sharing experience of specific discontinued trial)*

Researchers were divided in their opinions on how to foster meaningful collaborations. A few were of the opinion that eventually it is a personal style and ability of a principal investigator to connect with other researchers. Some principal investigators can do it naturally and are often successful in fostering collaborations. But others argued that collaborative clinical research should not be solely based on personal relationships established by the principal investigator with other colleagues as it is not sustainable in the long run. Such trials run the risk of collapsing when the principal investigator moves to another institution or

gets busy with another trial of higher interest. This is where academic recognition, competition, and award systems come into play as explained by one respondent.

"..... we need fewer researchers but better quality researchers. The way academia in medicine is set up, at least in Switzerland, is wrong. Somebody who wants to pursue a hospital career or wants to become a clinician leading a division in a university hospital or in a regional cantonal hospital; he or she has to do research to show that he or she is an academic. I think this academic model is outdated. I think it would be much better if we have very skilled clinicians who know how to apply clinical research and do an excellent clinical job and few researchers who first of all do not necessarily have to be MDs, they can also come from other fields who do really good research and are well trained. If they are really good, then you have to develop career possibilities and funding for them and that is also not sufficiently done here in Switzerland." (R8 Swiss trialist)

The system of promotion, recognition and career growth makes researchers focus on their individual work and the role as a principal investigator. But to be able to recruit patients in a large multicentre trial across Switzerland, one needs effective and functional collaboration across different centres. This requires a different set of skills and qualities but, as expressed by one respondent, these skills and qualities are not valued enough in the current system of academic evaluations.

"... (here in Switzerland), it's not usual that the university clinics, the centres with certain specialties, combine to undertake multicentre trials because everybody fears that he or she will not get enough benefit. The smallness of the university clinics and the individualised nature of people and centres refrain them from sitting together and collaborating for a multicentre trial. If, for instance, succeeding in a multicentre trial would be evaluated with additional added value... credit; that would be something which is beneficial for the CV of an individual that he successfully participated in a multicentre trial. And if participation is not diluted, it's even almost the opposite. This would change mentality quite a bit. I think even for the SNSF. It's not a priority to perform multicentre trials and to foster, to encourage collaboration between centres. In the Swiss context, the individual wants his career and thinks 'If I contribute to a multicentre trial, my own ambitions are not fulfilled.'" (T9 Swiss trialist sharing experience of specific discontinued trial)

Theme 4: Participant/patient-related factors:

Switzerland with its population of about 8 million and a comparatively high hospital density poses peculiar challenges in participant recruitment for RCTs. All interviewed principal investigators highlighted this fact and linked it to better access to healthcare and near saturation of therapeutic options for most diseases as described below.

"I think if we would have performed this trial in Romania or wherever in another country where the health care system is not as well developed, then it would have been easy to do it. Because it would be attractive to get this high quality care and we could have recruited very rapidly enough patients. I think it's particularly a problem in Switzerland when you do a clinical trial that patients have already access to a very good healthcare system. This kind

of protocol is not suitable for Swiss patients. This kind of intervention is not ideal, not very adequate for Swiss patients." (T9 Swiss trialist sharing experience of specific discontinued trial)

Two respondents stated that, unlike in the United States, where patients and the general public demonstrate a comparatively strong drive and desire to be part of clinical research either for financial reasons or to gain access to healthcare which is otherwise inaccessible or unaffordable, universal health coverage in Switzerland and availability of many treatment options covered by health insurance provides no incentives for patients to be part of clinical research (R9 pharmaceutical industry representative and R29 representative of FOPH). The situation is slightly different for Swiss patients with rare diseases but still not desperate enough to push them to participate in clinical trials (R16 Swiss trialist and R32 representative from Swissmedic). Half of respondents expressed their concern that many new drugs are tested not in the Swiss population but elsewhere, in eastern Europe, and that effectiveness and safety data generated through those trials cannot be easily extrapolated to the Swiss population. They advocated that the Swiss public and patients should engage more in clinical research to improve treatment options and not just benefit from the research which took place elsewhere. Six respondents further attributed the reluctance of the Swiss population to be part of clinical research to a negative coverage of clinical trials in the media where often metaphors such as "human guinea pigs" are used to talk about participants in clinical trials. Any catastrophes, such as deaths and severe injury of healthy volunteers participating in first-in-human trials in Paris in January 2016, are discussed in rather one-sided and sensational ways but other ongoing trials which are being carefully monitored and which contribute to improvement of treatment options are underplayed in media discourse, thus influencing general public in a biased way. All the respondents advocated improved engagement of the general public in clinical research and drug trials. The following quotation provides some suggestions to start such a process of engagement.

"I think all kinds of awareness-building activities that governmental scientific organisations could put in place to build awareness would be constructive. Clinical trials still carry the old stigma of using patients as guinea pigs. You know, to get over that, we could bring a new awareness to the culture, that science is for everyone and that we need everyone's perspective to become a healthier environment and better place to live! An idea would be to sponsor activities, research days, fun-family events, where information can be given out and people can learn about the concept of clinical trials and research and how clinical trials work and how they benefit society in general, and that in some cases it is very important directly for the patients (e.g., to be able to have access to new medications not yet on the market)..... Everyone knows about donating blood, right? That is really now an accepted and positive part of our culture. There are many blood-donation campaigns, sometimes conducted by hospitals, public health authorities, or even large employers. The same way that they do blood donation drives, you could do information dissemination about clinical trials. I think also talking in schools, going to science teachers and offering to explain clinical research would be informative and I think science teachers at

schools would welcome that. I am familiar with the public school system in the French speaking part of Switzerland and expect they would be delighted to have someone come and talk about research and science and to start giving information early to students.” (R26 Representative patient organization)

Discussion

Main findings

This qualitative study revealed that Switzerland – with its decentralised healthcare system, universal health coverage and availability of many treatment options for patients, little collaboration between different stakeholders in clinical research and underdeveloped research networks, many research regulations, often negative media coverage of clinical research, and lack of recognition for participating clinical researchers in large multi-centre projects – faces particular challenges for successful recruitment of patients to clinical trials. Limited human and financial resources, especially in the academic setting further aggravate the situation, and when funds are used up this typically triggers discontinuation of delayed clinical trials, which were once initiated with a great deal of optimism but insufficient preparation. Trialists and other stakeholders in the Swiss clinical research arena expressed the need for more interactive structures and collaboration across stakeholders to tackle the often interlinked problems.

Specifically, we argue that the funding and the human resources available for investigator initiated trials in academic research settings should be treated as a scarce resource. Though there are several recent initiatives and schemes from the SNSF and the FOPH (see below), they alone cannot make a difference unless there is clear prioritisation and research agenda-setting at the national level, development of research consortia and networks which undertake coordinated and collaborative research, rigorous assessment of feasibility of submitted research proposals, and continuous monitoring of clinical trials taking place in academic settings.

The Swiss healthcare system, funded and regulated at cantonal level, clearly influences the financing of hospitals in each canton and health insurance costs across cantons. The latter point is seen as a factor that limits the effective referral of patients from peripheral hospitals to the hospitals with ongoing clinical trials for the purpose of trial participation, but this discussion is beyond the scope of the current paper. Along similar lines, the decentralised ethics review procedure in Switzerland has limitations. In addition to the fact that protocols submitted to research ethics committees (RECs) often have scarce information on planned recruitment, members of RECs might also struggle to challenge the feasibility of proposals submitted by their colleagues/peers from the university hospitals. Federal level RECs specialised in different topics would allow review by experts in a particular field and could overcome challenges more efficiently. University and cantonal hospitals are in a strong position to undertake clinical research owing to the available research infrastructure, patients and research-oriented health care professionals, provided hospital administration perceives and promotes the benefit of research embedded in the clinical care set-up. Research can be easily perceived as an expensive activity (rather

than a revenue-generating activity), which could compromise the primary duty of healthcare professionals to care for and treat their patients. But hospitals can also take pride in their high quality research activities coupled with evidence-based health care provision, thus attracting researchers and healthcare professionals as well as patients. Large amounts of data collected by health systems when streamlined, stored and shared in uniform ways could significantly contribute to health systems research and to improve quality of healthcare provision.

Like hospitals, individual researchers need to balance their role in clinical research and care. Many young clinicians are interested in and driven by a research oriented mind-set to improve the quality of care they can provide to their patients, but they face a number of structural and career-related challenges. Structural challenges need to be addressed at national and institutional levels, otherwise there will be limited incentive and motivation for healthcare professionals to undertake research activities. As pointed out by a respondent, if only the first and last author publications count towards career assessment that is a clear hurdle for researchers to be part of large research networks and contribute to patient recruitment where they do not benefit themselves in terms of personal career development. We must point out that career assessment criteria need to be streamlined and clarified in an international context and not just in Swiss settings. This is particularly crucial in today's globalised research arena and highly mobile (in terms of geography and disciplines) research careers.

We do not argue or support the claim that lack of access to healthcare or misplaced belief that trial participation will provide therapeutic benefit should drive patients to participate in clinical trials. But we do believe that a change in mind-set of the general population, including that of patients, is needed in Swiss society. We cannot expect to benefit solely from research carried out in other parts of the world and built on contributions of patients from those countries, for two main reasons. First, with genetic, ethnic and general health profile variations in a population where particular drugs are tested, findings cannot be always extrapolated to other populations where a drug becomes available after licensing. Second, as a society we should also be willing to share the burden of research participation and to engage in the entire research endeavour from priority setting to research planning, implementation and dissemination of outcomes of research. There is also evidence that Swiss patients consider, on average, clinical research positively (see table 2 in [15]). We believe that researchers, clinicians, media and communication experts and patient groups have an important role to play. Finally, not every healthcare research study involves significant burden or risks, yet the willingness of a population and patients to share their anonymised medical data and personal information combined with a streamlined country-wide electronic medical record system could facilitate a vast body of research to strengthen health systems and to improve the health of patients and the population.

Strengths and limitations

The use of qualitative interviews with a broad range of clinical research stakeholders in Switzerland represents a major strength of our study which permitted to generate new and unique findings. The interviews provided real in-

sights into the lived experience of conducting clinical trials including the perspective of investigators whose trials were discontinued prematurely due to insufficient recruitment. Open-ended interview questions allowed respondents to elaborate on their viewpoints on how to prevent recruitment failure and to improve the Swiss clinical research environment in greater detail. We believe that the fact of having two interviewers conducting all the interviews in English and listening to each other's interview recordings improved the consistency and standardisation of the interview technique. Analysis of the interviews by generating codes and building themes was carried out by the research team to minimise systematic bias that could have arisen if the data had been analysed by only one researcher. Previous quantitative studies were limited in their exploration of risk factors for poor recruitment because their small number of variables allowed for a rather superficial view only [1, 16]. In addition, our approach overcomes problems of syntheses of qualitative evidence, that are frequently limited by the poor reporting of recruitment detail in the included trial reports and their inability to consider evidence from unpublished RCTs [12]. Our study adds to the scarce evidence base on how recruitment to clinical trials was planned and conducted in practice [5, 17]. We employed purposive sampling to access a wide spectrum of viewpoints that strengthened our findings.

However, there were 22 Swiss trialists and 4 other Swiss stakeholders who did not reply to our emails or declined participation. Whether the views of those 26 persons (40% of invited) are substantially different from those who were interviewed is unclear. Some explained their refusal by their extremely busy schedules and priority given to other tasks, but reasons may, at least in part, include the consideration that openly discussing and analysing failures is not popular in the research community. According to a recent cross-sectional survey in Switzerland, patient enrolment and logistical problems top the list of difficulties in clinical research in general – not only in RCTs [18]; i.e., the investigated difficulties with clinical trials could be the symptoms of a more general problem related to acceptance of clinical and population research in medicine, which, however, is beyond the scope of this study. Finally, to tease out particularities of the Swiss clinical research arena was part of the study aim inherently limiting extrapolation of findings to other countries.

Recent developments in the Swiss clinical trial context

Since we started conducting interviews for this study in August 2015 there have been recent developments at the SNSF and FOPH with promising initiatives that partially address some points mentioned by interviewed stakeholders who might not have been aware of those initiatives at the time of interview: (1) In August 2015 the SNSF launched a special program “Investigator Initiated Clinical Trials (IICT)” for the first time to enable independent clinical researchers to answer clinical questions that are important for patients [19]. The yearly budget of the SNSF for 4–8 industry-independent clinical trials is about CHF 10 Mio. (2) The recent SNSF initiative “Protected Research Time for Clinicians” (PRTC) is intended to help especially younger clinicians to dedicate at least 30% of their working time to their research project funded by the SNSF [20]. (3) A task force deployed by the FOPH de-

veloped the 2016–21 roadmap for building up the future generation of clinical researchers which is “designed to help close gaps in the career track for clinical researchers and provide them with opportunities for efficient high-level training” [21]. Responsibility for implementing the roadmap is shared by the local MD-PhD graduate schools, the SCTO with its network of CTUs, the Swiss Academy of Medical Sciences, the FOPH and unimesuisse. (4) The FOPH launched the Swiss National Clinical Trials Portal (SNCTP) that replaced a not user-friendly previous database for Swiss clinical trials [22]. The SNCTP displays trials submitted on the Business Administration System for Ethics committees (BASEC) platform in real time as soon as they are approved by the ethics committee. The FOPH further planned to add lay summaries and to continuously improve the utility of the tool.

Comparison with other studies and implications

Although various studies have already investigated barriers to and facilitators of recruitment [2–11], only one of these focused specifically on the Swiss context. A postal survey by Spaar et al. was conducted among 55 recruiting physicians of a Swiss multicentre trial on respiratory rehabilitation strategies in patients with chronic obstructive pulmonary disease [5]. Based on the 35 useable returned questionnaires they found that “time constraints” was perceived as the most relevant recruitment barrier by recruiting physicians followed by “difficulties including identified eligible patients”. These points were also evident in our interviews with trialists and were mentioned in surveys from the physicians' perspective in other clinical settings highlighting their general importance independent of a Swiss context [4, 23]. Moreover, high quality evidence on particular interventions aiming at patient recruitment is sparse and more methodological empirical research embedded in clinical trials is needed [24–27]. Another report by Weisskopf et al. suggested a set of tools in the clinical information system of the University Hospital Zurich that may (among other advantages) also improve the planning and conduct of patient recruitment to trials [28]. This initiative and the already mentioned recent developments of new support programmes by the SNSF and the FOPH are promising; however, the effectiveness of the new programmes and initiatives needs to be evaluated with quantitative and qualitative indicators in order to allow confirmation or change of strategies. We believe that further large collaborative efforts across various stakeholders in clinical trials appear necessary to sustainably improve patient recruitment in RCTs in Switzerland. All stakeholders seem to agree on the importance of the problem but it seems less clear whether they are prepared to take further responsibility and action in a commonly agreed collaborative plan.

Conclusions

This exploratory analysis of 39 interviews with Swiss trialists and other stakeholders on reasons and potential solutions for insufficient recruitment of participants to clinical trials in Switzerland revealed various country-specific particularities that contribute to the problem and are mainly related to four themes: the healthcare system, availability of funding, roles and attitudes of investigators, and the participants' perspective. In addition to recent promising developments at the SNSF and FOPH, agreement on com-

mon goals and concerted efforts by the involved stakeholders appear necessary to achieve improvement.

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Competing interests

All authors declare no conflicts of interest.

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Appendix 1

Interview guides

The interview guides are available as a separate file at <https://smw.ch/en/article/doi/smw.2017.14556>