

First in Human

Who and what makes a cancer phase 1 trial and why are they so important?

Report

Please cite this project using the following DOI:
[10.17605/OSF.IO/KWHQF](https://doi.org/10.17605/OSF.IO/KWHQF)

Phase 1 clinical trials assess new cancer treatments in people for the first time. Bringing new cancer therapies into routine cancer care is a long and complex process. It is a critical step in the pathway. The aim of this project is to define and communicate the world of a cancer Phase 1 trialist, and the value they bring.

Through a deeper understanding and insight of those involved, we hope this will benefit those interested in careers in cancer clinical trials, stakeholders and partners seeking to innovate across the cancer control continuum.

Phase one trials are small in scale, with a limited number of patients. These trials usually recruit patients who have exhausted other treatment options.

The aim of phase 1 trials is to explore doses and side effects. Trials don't offer benefits to participants - However, other people may benefit from the new treatment in the future.



For any information, please contact:
Gaston Welisch - gastonwelisch@gmail.com
Nicol Keith - nicol.keith@glasgow.ac.uk

Table of contents

6

The Importance of Phase 1 Trials

- Gatekeepers
- Enabling Future Therapies
- Human centred
- Small Scale
- Limited window of opportunity/urgency
- Reputation/Trust

10

The Impact of COVID-19

- Resilience
- Patient experience
- Networking remotely and the value of face to face contact
- Accelerating change
- Visibility of Trials in the public eye - highlighted value

13

Who makes a Phase 1 Trial happen?

- Lifelong learning / curiosity
- Dealing with Uncertainty
- Communication
- Empathy
- Evidence based

16

Networks and Stakeholders

- Lifelong learning / curiosity
- Dealing with Uncertainty
- Communication
- Leveraging / accessing different expertises
- Avoiding silos / defragmentation

19

Learning from treating childhood cancer

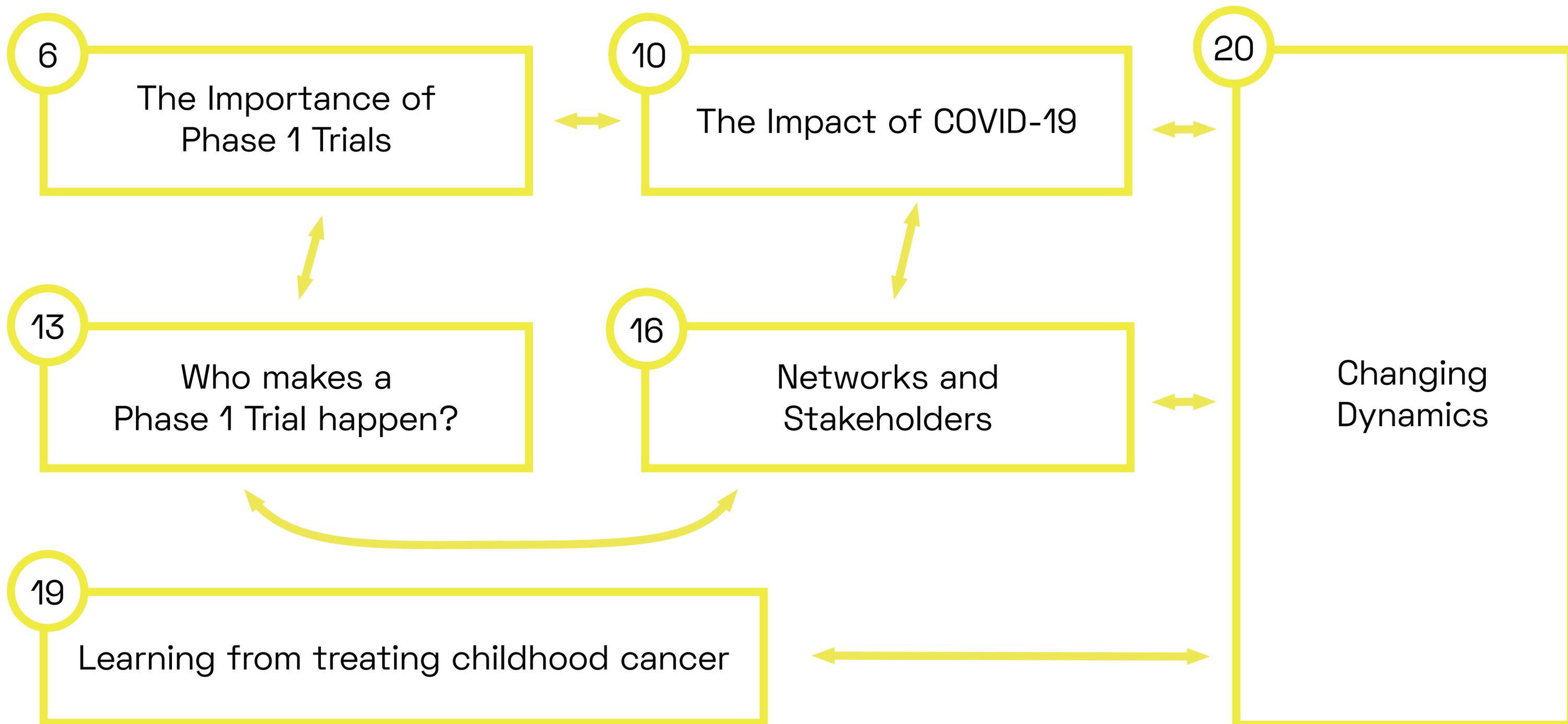
- Changing population
- Redefining quality of life, and how it's measured
- Side effects

20

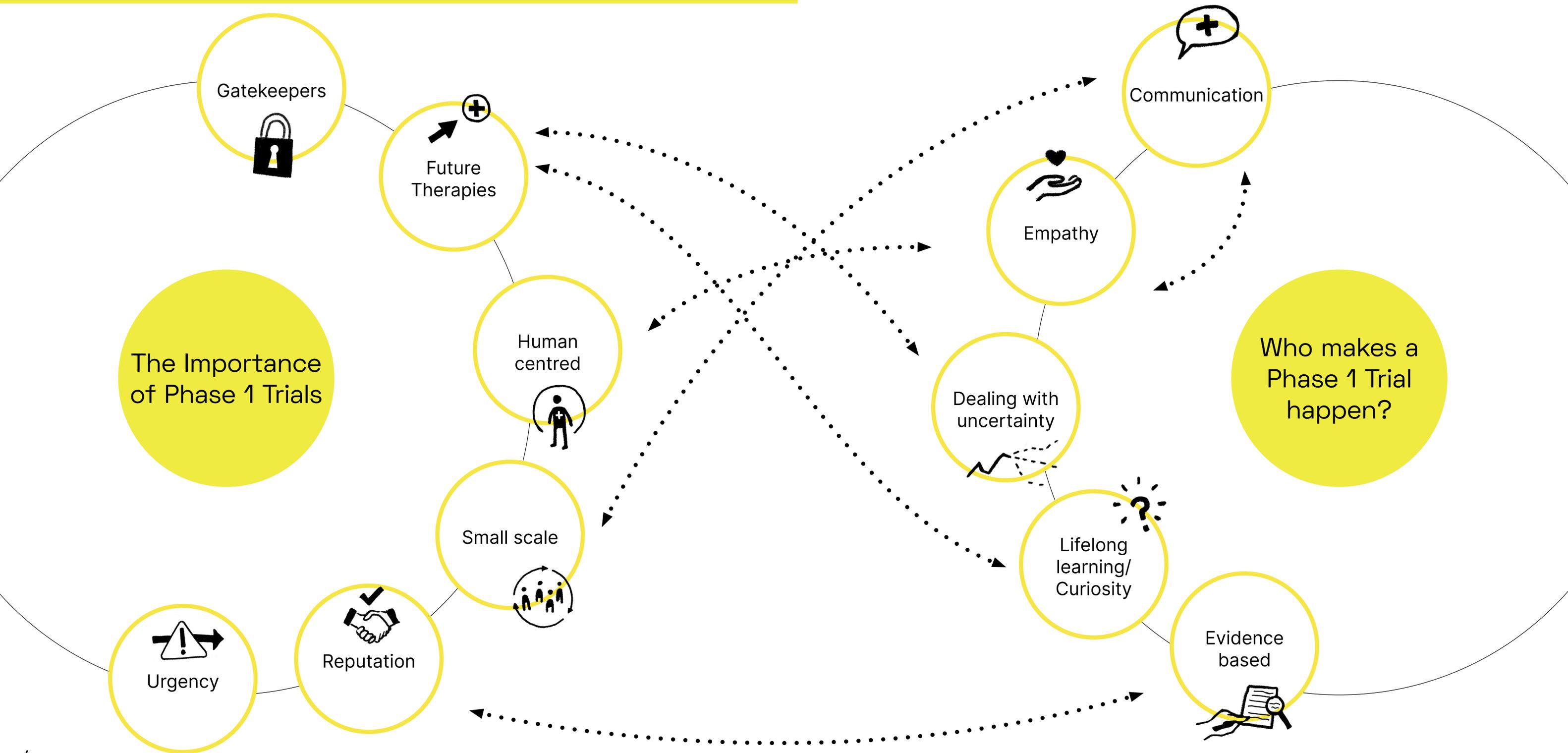
Changing Dynamics

- Patient involvement in trials
- Changing Population
- Growing size of studies and competition
- Electronic Data / Knowledge Management
- What's next?

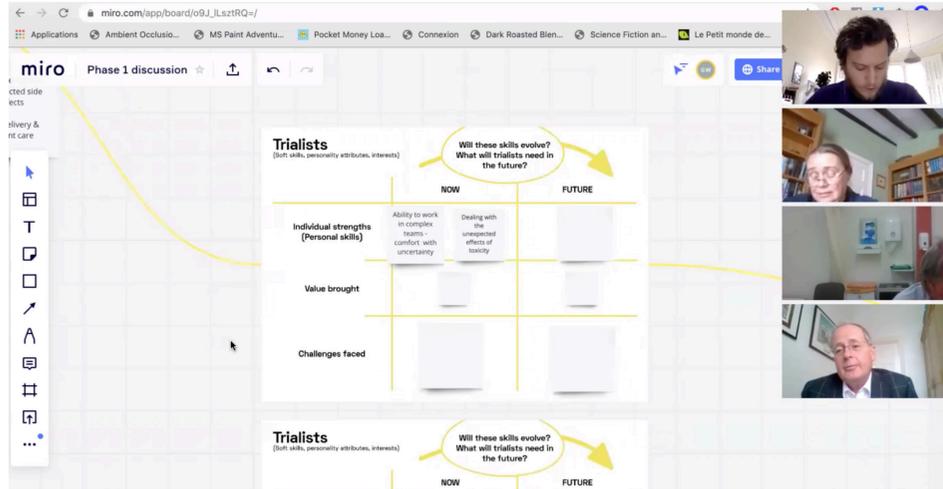
Table of contents



Graphical abstract



Know-how



A community of senior and early career oncologists were asked to participate in group consultations and individual interviews to reflect on the importance of Phase 1 trials, who makes them possible, the value of networks, and the challenges and opportunities presented by the COVID-19 pandemic. Over the following components, you will see quotes and summaries of what emerged from these sessions.

The participants' discussions were written down during the sessions using a digital collaboration platform (Miro), and were then also transcribed using the recordings. For the analysis, we focused on important recurring themes, classifying them within the structure used during the consultations.

Cancer experts were pooled from the UK Experimental Cancer Medicine Centres (ECMCs) network, Clinical Trials Units and University Cancer Institutes as well as internationally from Malawi. Participants ranged from early career clinical fellows to senior clinical academics and research scientists. Expertise ranged from phase one specialists, heads of clinical trials units, and childhood cancer specialists.



The importance of phase 1 trials

Phase 1 trials safeguard cancer patients and enable future therapies with empathy. Participants were asked about the particularities of phase 1 trials in cancer specifically, and what makes them special.

GATEKEEPERS

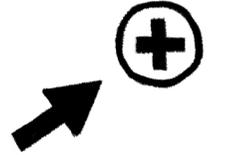


Phase 1 trials safeguard the patients by gatekeeping the drugs and treatments that have unacceptable toxicity or limited efficacy.

“(Phase 1 trials are) the infrastructure within which to learn. It’s not just about recruiting the patients and collecting the data. It is the understanding of drug action that can allow you then to make sensible decisions about taking the drug forward into later phase trials.”

“(…) saying, look, I think we should drop this drug now because either from an unacceptable toxicity which cannot be overcome by any other strategy, or because of lack of efficacy and being brave enough to say, just pull the plug on this drug at this point now, or I don’t think this one’s going to go forward in (a) competitive environment.”

FUTURE THERAPIES



Phase 1 trials enable promising future treatments to go forward into later phase trials by being the first step of testing in human patients.

«If there are good new drugs coming through, and we have seen a huge number of really powerful and cheap practice changing drugs come through in the last 10 to 20 years, what you want is as fast as possible, that we get access for patients within the health service. And there are lots of factors that play into when those regulatory processes go through. And having active clinical trials and clinical research is a really important starting point for a country to keep its health service moving forward.»

«Almost all of the patients we talk to get the fact that if they don’t benefit, somebody else might.»



URGENCY

There is a limited window of opportunity for patients to take part in Phase 1 trials, so it is important for patients to be aware of their options at the right moment.

“And one of the challenges we have when patients are running out of treatment options is whether their attending clinician says to them, we’ve run out of treatment options. And things are likely to get more difficult. Do you want to think about a trial? Or whether the treating physician simply says, well, we’ll give you a break off treatment at the moment and see you in three months time? And if you do the latter, then the window for an early clinical trial may well have closed or be much more limited?”

**HUMAN
CENTRED**



“ We ask the patients with terminal cancer if they’re prepared to take an experimental drug, where we don’t know the dose and we don’t necessarily know the side effects. ”

Patients in phase one trials are usually terminal and have exhausted standard treatment options. These trials are very intensive and challenging for patients, especially since they may already have had a long cancer journey at this point. Being part of a trial means more hospital visits, procedures and commitments. Trialists need to be open to patients to gain informed consent, explain that they are not offering benefits and make sure the patients understand the implications correctly and that the trial is right for them.

“I used to invite the administrative staff into the clinic, basically, so they could see (that) this isn’t just a paper or electronic exercise. So I think that you (need to) appreciate seeing the patient facing side of things.”

“(There is) this balance between not destroying hope, while not encouraging unrealistic expectations, being able to transition them so that you’re providing both the supportive care that they are going to need, if and when they leave the clinical trial.”

“I think it’s a special and different relationship with the patients. And the level of gratitude of patients is really humbling.”



REPUTATION



SMALL SCALE

The smaller scale of Phase 1 trials creates a unique dynamic, not found in later phase trials. Oncologists get to know the patients better, which is important on a human level, but also gives the opportunity to develop pattern recognition to spot subtle unexpected side effects or toxicity. Trialists also get to have an important impact on the development of new drugs and treatments at an early stage.

“We tend to see the early phase trial patients more frequently. So we tend to be a smaller team looking after the early phase trial patients so others see if they’re agreeable, I find myself getting to know these patients better.”

“So there is a more intimate relationship with the development of a drug and the ability to shape how that drug is developed. The proximity to the action, and the sense that you’re dealing with something that is genuinely novel, you’re giving a chemical to people with cancer in the last few months of their lives, a chemical that looks like it’s okay in mice that hasn’t been given to people before. It is actually fairly mind blowing when you stand back and think about it.”

“Pattern recognition is important, because the way we set up these studies, rather than everybody doing them, you have them concentrated in a small number of investigators and a small number of centres, so that they see the multiple patients getting treated with the same trial. So they have the opportunity of seeing that unusual, unexpected pattern recognition toxicity that would be diluted if a study of not very large patient sample size was diluted across too many centres.”

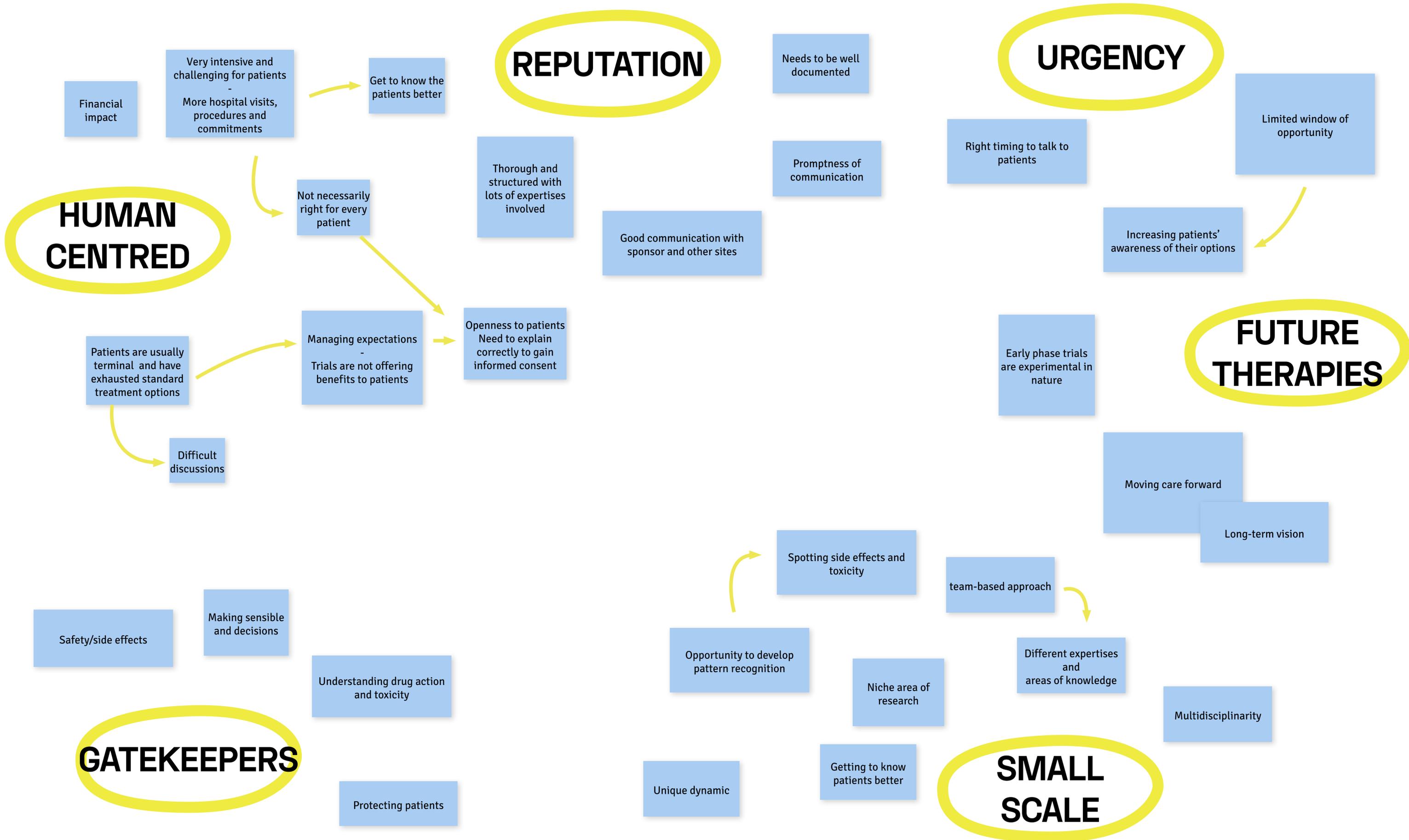
“If each centre only sees one or two patients, you lose the opportunity for pattern recognition.”

A centre is only as good as its last trial. Sponsors rely on the reputation of centres to form relationships and trust them with their trials.

“It’s a competitive business internationally to attract early phase trials to your centre, because we want opportunities for our patients (...) And there is a reputation that has to be acquired and maintained. And you know, they say football is only good as your last game, we’re only as good as our last trial. If we foul it up, that sponsor is unlikely to come and approach us anytime soon afterwards. So I think there is a reputation that comes from building up a critical mass of early phase trials in your centre, that you can convince people who have invested an awful lot of money to develop this novel compound to trust you with its development in the critical phase and early phase trials.”

“It’s about maintaining that relationship. And that comes down to whether you recruit the way (you said) you were going to do it, and whether you provided the data in a timely manner. Did you follow the protocol? Were there any concerns and serious protocol deviations?”

“(Something that is) emphasized in terms of building up a trials department and having commercial relationships with pharma is punctuality and robustness of communication. (...) And the more robustly you deliver their trial, with good assessments and good documentation, then the more likely they are to come to you with another trial.”



The impact of COVID-19 on phase 1 trials



ACCELERATING CHANGE

For this, participants were asked to share and reflect on their individual experiences during the COVID-19 crisis, as well as the long term impacts it would have on both the patient population and the people working in the field.

They were then asked to identify the challenges and opportunities brought by the crisis and the adaptations that had to be made.

RESILIENCE



COVID-19 has highlighted the resilience and adaptability of cancer trialists and their network to continue patient support in the context of global disruption.

“There has been some positivity, I think I think it taught us all (...) how resilient we actually are.”

“If you look at the practice of oncology, it’s constantly changing, we’re always bringing in new therapies, new drugs, improvements in care. And one of things really impressed me about the pandemic is actually that progress has continued despite the pandemic. We’ve introduced new drugs, we’ve introduced new ways of treating people.”

PATIENT EXPERIENCE



There is a worry that the delayed diagnosis of patients, and the adaptations made during the pandemic will have serious long-term consequences that will be felt after COVID.

“So there will be patients that have had delayed diagnoses, and they will never get the treatments that they should have gotten. There will be delays, or there’ll be reduced numbers of trial options for a cohort of patients. They’ll be companies that don’t come to where they perceive high incidence of COVID to be, which obviously includes the UK, so they’ll be missing out on trial opportunities. I’m worried that some centres will lose most of their trial activity, because they weren’t able to get funding from things like the cancer charities. And I don’t think patients will want to travel in the same way that they used to. And, you know, then the patients may not want to be treated in the same way. So they might not want to have as many appointments and as many scans and maybe clinicians won’t want to do that either.”

Remote consultations have reduced travel time for patients seeking to take part in trials. Other measures, such as local blood tests and drug delivery, have been put in place for the benefit of patients.

Digital meetings have bridged silos by enabling people who would not usually be part of panels/meeting/talks, such as international collaborators or people from different disciplines, thus lowering the barrier of entry. Finally COVID-19 has highlighted the value of networks, as trialists leveraged international connections to get quick and accurate information about the virus and safety for patients.

“We’ve had, in an effort to kind of keep everyone updated and connected, a lot more meetings, and virtual meetings, not necessarily just within the group, but within the institute. And people can understand what other groups are doing. And so there has been a lot more kind of drive to kind of stay away from these silos, where you don’t know what’s going on within your own Institute.”

“And I think we really used our paediatric networks right at the beginning. So you know, we didn’t know whether children with cancer were going to be affected by COVID or not. So we literally just picked up the phone and emailed our colleagues in Italy, and in China, and just said, “Have you seen lots of cases?”. we didn’t have to wait for it to come out. And so actually, we had reassurance really quite early on in the pandemic, that there wasn’t going to be a major problem, because we literally had the paediatric oncologists from EU saying, “we haven’t seen a big problem”. So there’s, I think our paediatric networks really, really helped us at the beginning, although obviously, we still had to take all of the precautions.”

NETWORKING REMOTELY



COVID-19 has disrupted networking and communication, forcing rapid adaptation in switching to remote meetings and conferences. Whilst some opportunities have been missed, such as serendipitous chats in hallways and in conferences, trialists recognise the need to adapt to the circumstances and create new modalities of networking remotely.

“It’s all about collaboration. It’s all about talking to people, it’s all about networking. And, yes, there is a definite need and role for face to face meetings. But of course, you can never get everybody you want at a face to face meeting if they have to travel for days to get there. Now, there’s no excuse if you can get much better attendance when the whole meeting is on zoom. I think the really valuable lesson everybody has finally learned is that virtual meetings don’t work if half the people are real, and half the people are virtual, everybody has to be on an equal footing at the meeting. So I think we will have a clearer understanding of this meeting would be better run virtually, this is the meeting that needs to be face to face. And therefore will be able to be more inclusive, you be able to get the right people at the meeting. And it enabled us to have to and to interact differently, and hopefully to interact better. You know what the meeting behaviors interactions are different when you’re on a zoom call. We mustn’t assume that they’re all better.”

“One of the things that really worries me actually is virtual meetings, and working from home, are they fine as a sticking plaster? We thought this was done and dusted in three or four weeks, everybody went home with a laptop, sitting in their office at home, works fine for a few weeks. But if it’s permanent, then you do lose stuff. And these things will be permanent. And what really concerns me is, it works fine for me, because I’ve spent years building a network of people who do the work I do, I know who to talk to, I know how to deal with individuals. And then in 10 or 15 years time, they’ll be nobody who was here before. So how do we bring in new people, how do the new starters, the young, the new talent, build those networks? How do they know who to talk to? I’m not saying they have to do it the way I did it. But what we’ve put in place is sticking plasters. We’ve not put in place systems to build networks. And so we have to really think about that, and how we bring in new people. And it’s not just about training, it’s about those less tangible things around networking, and that’s really, really important in clinical trials research.”

“(Networking has suffered during COVID) because you’re not having those opportunistic meetings with people in the corridor of a conference, or we’re looking at the same post or whatever. But it hasn’t completely eliminated the opportunities to network, you still form them by knowing people through projects you’re working on, and being proactive in terms of engaging with sites where you already have involvement and getting to know the people who work there, but also they introduce you to other people. We’re going to go to fewer face to face conferences in the future. No matter what happens in the next six months or a year, people are going to go to more online conferences, because it’s cheaper, it’s more efficient with your time, it’s better for the environment, etc. We all have to think about our strategies for how we’re going to network in a new world where we’re leaving our house a bit less.”



VISIBILITY OF TRIALS

The COVID-19 vaccine trials and the quick development of the vaccines has highlighted the value of trials in the public eye, and given a clear example of impact that trialists can refer to.

“I think if we can build on that, it will be great. Because we now have very concrete examples of how trials helped care in a very short time. I think it’s different, more difficult with cancer, where we found this target 20 years ago, and we found the drug 10 years ago, and then we did these trials, whereas it’s very condensed, the examples that you can give for COVID research.”

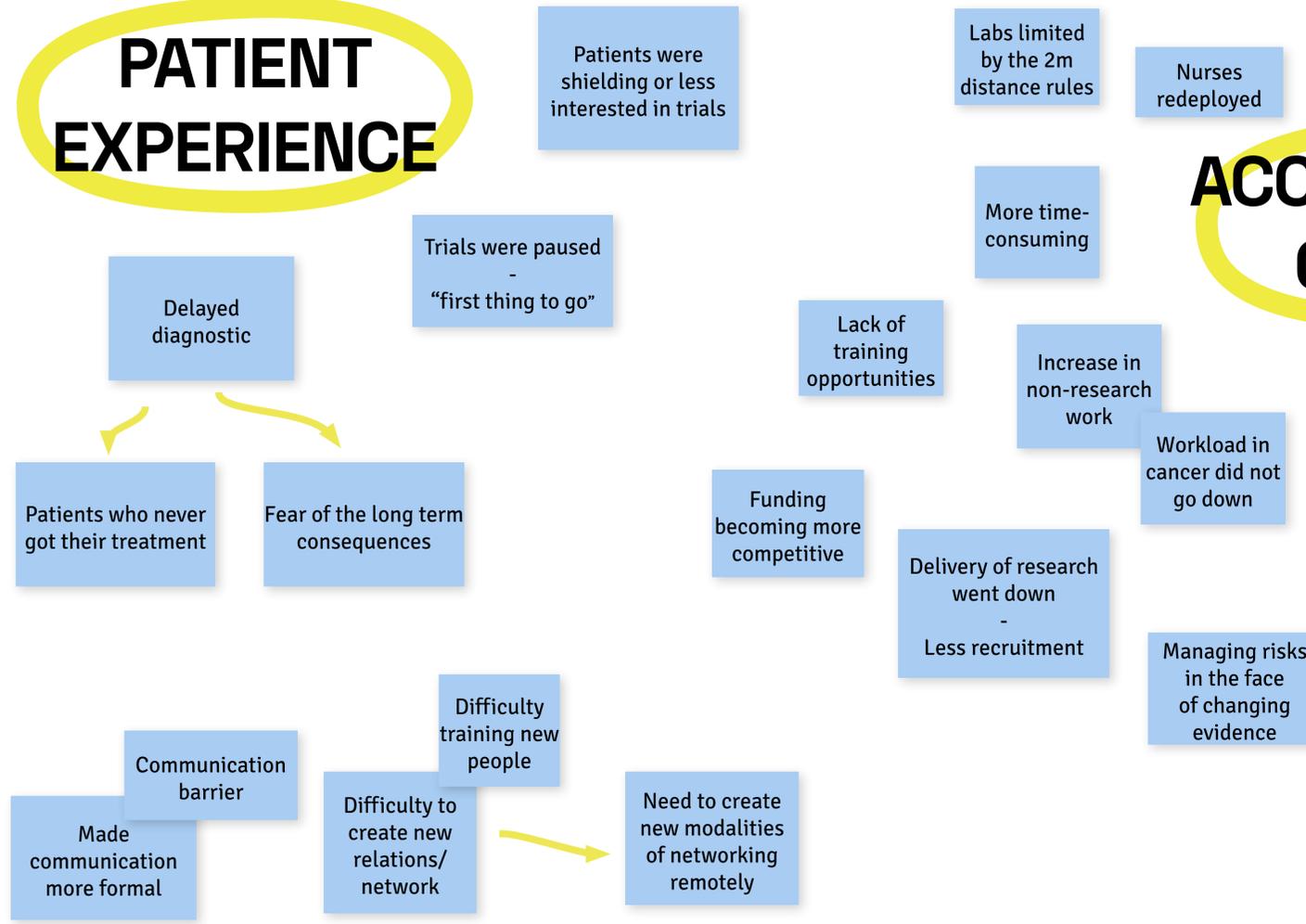
“I suppose the general public will better understand better what we do and then support their families to make those choices.”

“We’ve had examples of vaccine developed through clinical trial. If you want to think about trial impact, you’ve got basically an amazingly impactful number of trials, showing you how it can be done.”

Challenges

“What changes or adaptation has been put in place as a result of COVID-19 that you are worried about/ are looking forward to get rid of”

PATIENT EXPERIENCE



NETWORKING REMOTELY

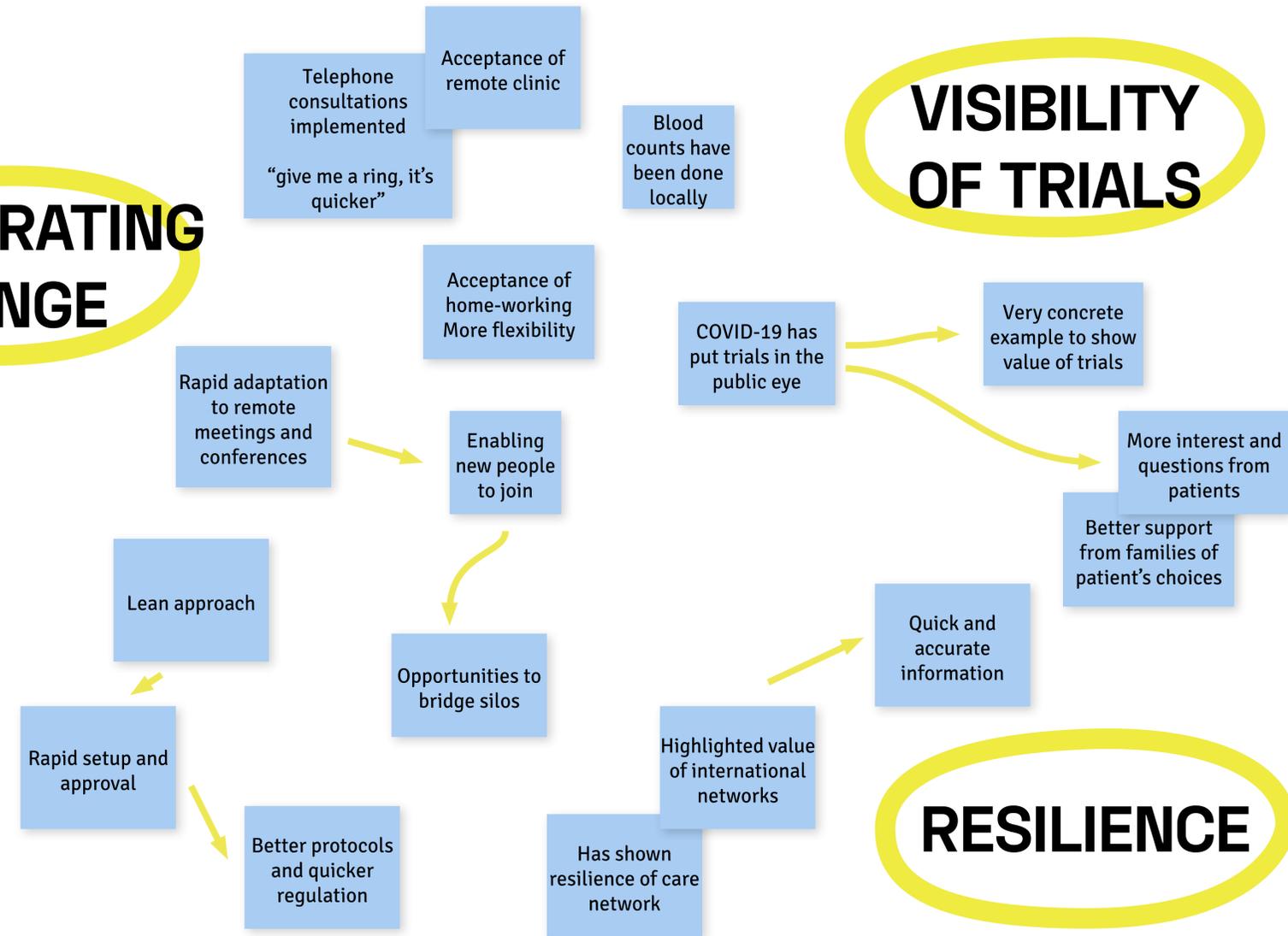
Missed opportunities
Miss having people around for troubleshooting

“ There’s something lost in the fact that you can’t have face to face conversations with people. Certainly with younger trainees, like myself, if you’re on an online meeting with 50 or 100 people, you’re not going to speak out and say something, whereas if you had the opportunity to really speak to some of them over coffee, you could build up your relationships. ”

Opportunities

“What changes or adaptation has been put in place as a result of COVID-19 that you hope will stay”

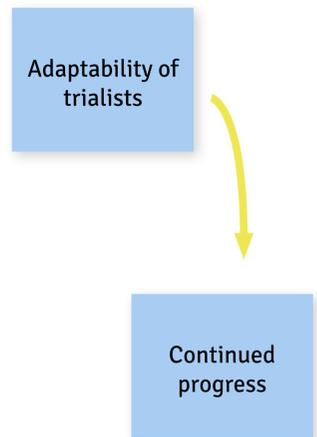
ACCELERATING CHANGE



VISIBILITY OF TRIALS

RESILIENCE

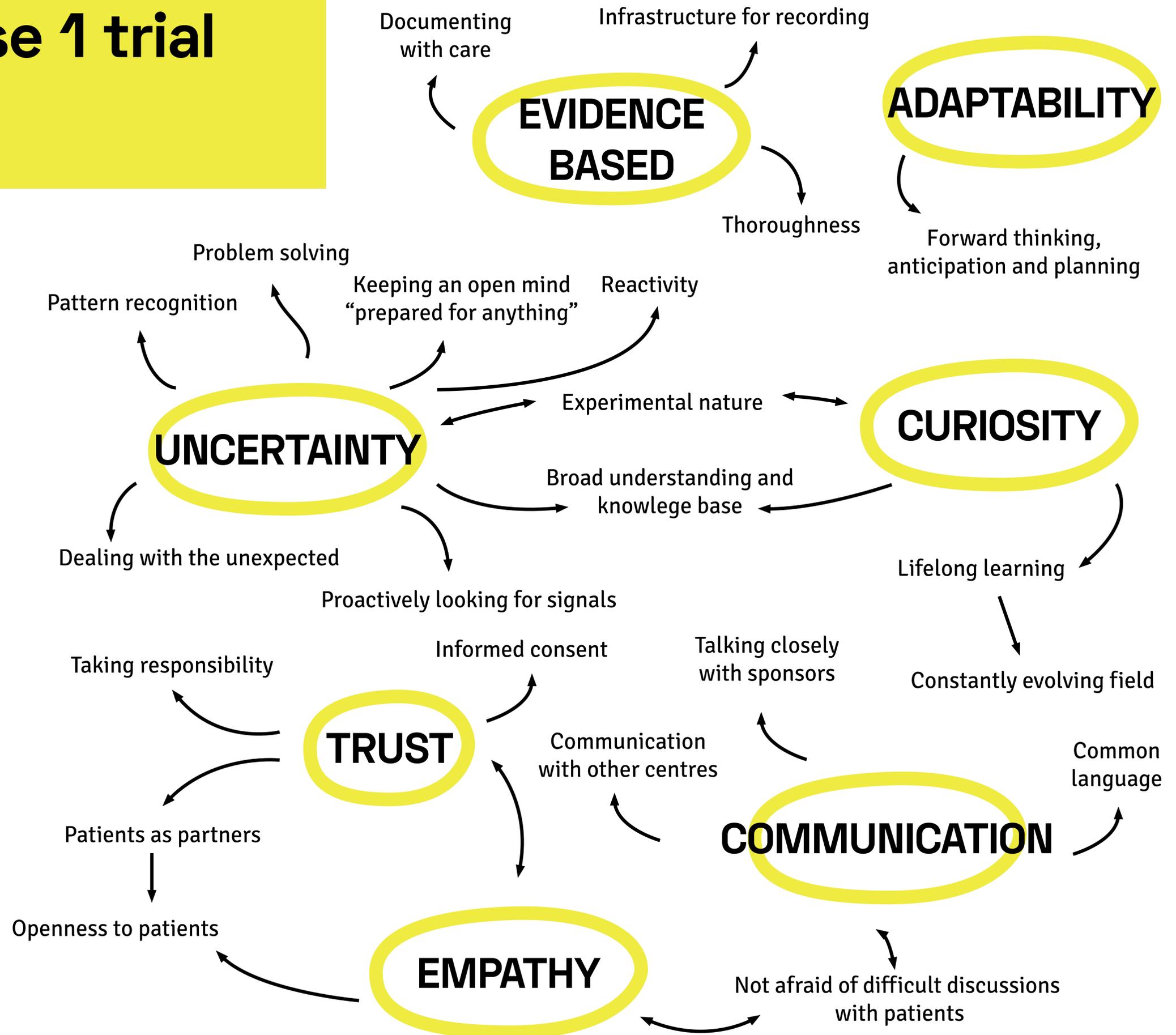
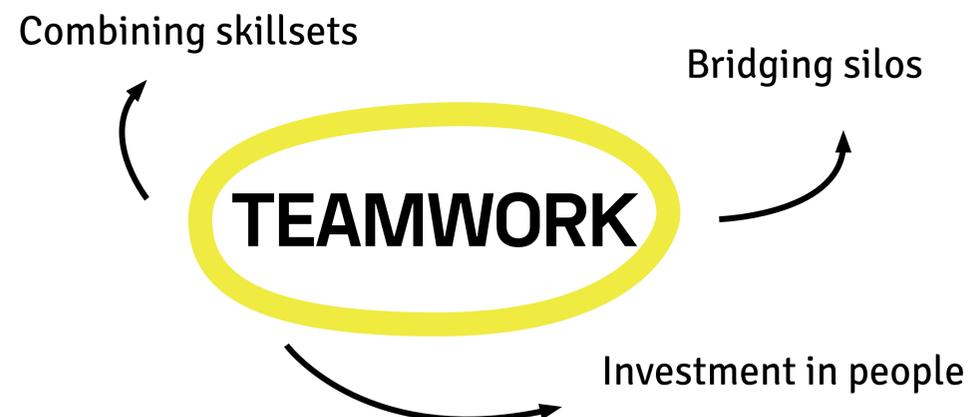
“ If you look at the practice of oncology, it’s constantly changing, we’re always bringing in new therapies, new drugs, improvements in care. And one of things really impressed me (...) is actually that progress has continued despite the pandemic. We’ve introduced new drugs, we’ve introduced new ways of treating people. ”



Who makes a phase 1 trial happen?

“It’s my responsibility if things go wrong, and I would be very uncomfortable devolving that responsibility to anybody else.”

A community of senior and early career oncologists were asked to pause and reflect on what experiences, values, behaviours, motivations, skills, mode and style of thinking, shape a successful cancer Phase 1 trialist. Participants were asked about the skills and experience needed to be a trialist. The aim was to define the philosophy of people working in trials, their strengths and the value that they bring.



CURIOSITY



Cancer is a constantly evolving field, with new drugs, new treatments, new ways of working
Trialists are curious people who keep up to date with changes and learn from others.

“We’re all going to need to have a lot more knowledge. As we go forward, you know, the science is becoming more and more specialized, and some of the side effects are really different for different types of drugs. So I think there’ll be a much bigger piece going forward about education, (...) People will need to be highly motivated and clever to be able to keep track of all of that.”

“I think it’s important to have the ability to first of all challenge the status quo. (...) It’s about being able to identify where the tangible unmet needs are.”

DEALING WITH UNCERTAINTY



Due to the experimental nature of Phase 1 trials, trialists need to proactively look for signals in patients and have good pattern recognition to spot unexpected side effects. They also need the clinical and problem solving skills to then deal with these side effects appropriately.

Trialists keep an open mind and stay “prepared for anything”.

“I remember a little while ago, sitting with a patient, who had no toxicity from the previous cycle of treatment, but just was blinking and just looking slightly strange. And I’d asked her if her eyes were sore. And she said, No. So it’s just, it’s just these flashing lights that I’ve started seeing. And so picking up these side effects, we have an idea what the side effects may be, but we’re also more and more looking for unexpected side effects, and being open to those and having the clinical awareness to hopefully identify them, I think is important.”

“You need to have a pretty broad knowledge of medicine, to deal with unexpected side effects and good problem solving skills. There’s also telling apart toxicity from disease and from comorbidity as it’s important to understand what’s drug related, and what’s not.”

COMMUNICATION



Communication is a key skill for working in early phase cancer trials, to collaborate with colleagues who have very diverse skills, coordinate with other centres, as well as talking closely with sponsors. Cancer trialists are also willing to have difficult discussions with patients.

“It’s in the nature of those trials, that you’re being very open with the patient about their their situation, the limited likelihood of benefits, the stage of their disease. It’s these conversations, which we welcome, which many colleagues may actually feel that they would prefer to avoid. (...) We tend to see the early phase trial patients more frequently. So we tend to be a smaller team looking after the early phase trial patients (...) I find myself getting to know these patients better.”

“One of the challenges I feel in the clinic is when patients come to see me as they will tomorrow morning. And they know they’ve got no treatment options left. They might agree with anything I suggest. However, unreasonable, uncertain, time consuming it is. The role of the research nurses in talking to patients and making sure they understand properly about the trials and aren’t just saying yes to anything”

“Clinical trials are probably the absolute epitome of teamwork and communication, because there’s so many different highly skilled individuals involved. And so to tie up the whole thing, everyone needs to talk to each other in a language that the other person understands. So I suppose this practice and awareness of what the colleagues’ scope of skills and language are to then tailor your (communication) accordingly. And you want to communicate effectively so that everyone feels part of the team and (it) is easy and efficient.”

EMPATHY



EVIDENCE BASED



“Because at the end of the day, if it’s not important to actual patients and the public, then it’s probably not something you should be focusing on.”

Trialists are driven by wanting to improve care, and they see patients as partners. Openness and empathy are important skills to use at all times so that trials are designed and conducted in the most humane way possible, and their implications are made clear to patients. They take responsibility of their actions.

“It’s about a drive to want to make things better, and to understand what would make a patient want to participate in a trial. But it’s also about being able to give patients sufficient information that they can make an informed choice of what’s right for them. (...) You’ve got to want to seek to do better. You’ve also got to want to really understand what the patients want, which is often very different from what the investigator wants to do. And sometimes that can be really challenging bringing those things together.”

“(Amending) dosing protocols can really help (patients) with their treatment, and that brings satisfaction. You might be monitoring a patient who’s getting excessive toxicity, because they’re being dosed too high. Being able to (monitor drugs) is pretty great, because you’ve had some impact and can have impact for future patients as well, so that they don’t have to go through kind of excessive toxicity, or have the potential of being under-dosed.”

The complexity and uncertain nature of Phase one trials requires trialists to be thorough throughout the research process and document with care and insight, ensuring evidence is recorded appropriately. Trialists bring their experience, insight and interpretation to complex data.

“Everything needs to be very well documented in everything that you’re doing, whether it’s taking samples, sending samples, noting adverse reactions or toxicity or response. If you want to make sense of what’s coming out at the end, it needs to all be well recorded. Sometimes just small things, like even the units of a dose might be wrong, that someone’s written down, and then kind of the interpretation of that later, can really impact your findings.”

“It’s about being very thorough, good documentation, following things through, but also being prepared to go into the unknown. With these new agents, I think you’ve got to know a bit about a lot of things. You need to know about if you’ve got a patient with a specific tumour type coming through, you need to quickly get your head around how their treatment pathway may have been, regardless of where they’ve come from. You need to be prepared to do a bit of background digging. You need to very much know the evidence that’s that’s coming through about different types of drugs and approaches, so that you’re not just thinking of your one particular trial, but might see patterns that have developed elsewhere.”

Networks and stakeholders

How are networks created and how do they evolve? Creating an optimal dynamic, leveraging skills and experiences by reaching across silos through curiosity and informal links.

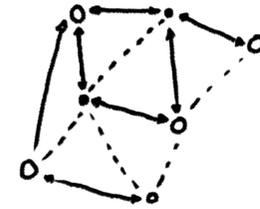


INFORMAL RELATIONS AND CURIOSITY

Creating and maintaining networks requires making the effort to stay aware and curious of new things happening and reaching out to people. A large part of creating these networks is also the trust and reputation you have among peers.

“We often informally email people to say, you know, to ask advice or to ask, you know, have they got a trial for a patient?”

“In terms of establishing that network in the hospital, you are inheriting from those who were there before, but you won’t get any referrals from your colleagues unless you have credibility as a clinician and as a clinical researcher or somebody who’s going to take care of their patients.”



LEVERAGING EXPERTISES

Networks enable cancer professionals to exchange, integrate and share data, insights, knowledge and expertise in a collaborative manner contributing value and learning to all involved. Importantly they provide peer support. This dynamic stimulates network-wide effects, building, embedding and spreading excellence within a community of practice.

“I think (The ECMC network) has worked effectively to allow better referral of patients and better sharing of data. And I think that’s been taken up by the network as a whole. And we’ll be used as an example, going forward. And so we’ve all got different areas of expertise, we’ve got different patient populations. So it’s really about working together in collaboration rather than competing with each other.”



SMALL SCALE

The scale of Phase 1 trials makes networks especially important to share information and identify patients.

“I think that’s also why we say we’ve got these wider link networks, whereas if you’re the huge juggernaut of a phase three, as a breast cancer doctor or a melanoma doctor, you don’t need a big network (...) to get, you know, the big trials come along, and they approach the centres. But we need the smaller interacting networks to identify the rare patients for precision medicine trials, the networks to attract trials in and the networks of people to work with. And then the complexity with some of the new treatments, we need networks within the hospital, to be able to give these cellular therapies and do it safely.”

AVOIDING SILOS



Learning from others and sharing experiences and knowledge optimises time and is an accelerant for progress. It is important to keep a good awareness of the field, and a lack of understanding between stakeholders can be detrimental. Defragmentation and the breaking down of silos helps with organizational understanding and develops a respectful space for communication, learning and knowledge exchange.

“Because, you know, we all work in our little silos, but sometimes you don’t realize until you know, by chance here that someone half a mile down the road, does something exactly the same or has done before.”

“We’re all academics who work in universities. And it’s a mixed bag where they really understand what we do (...) I get frustrated sometimes being at senior management meetings when they say, well, clinical trials is just doing your day job (...) And it’s not that they don’t understand the reputational benefits and the infrastructure required, some do, not all people do. And I think (we need) continual education of ourselves and our colleagues.”

* Global perspective: Malawi



GLOBAL PARTNERSHIPS

BRAIN DRAIN

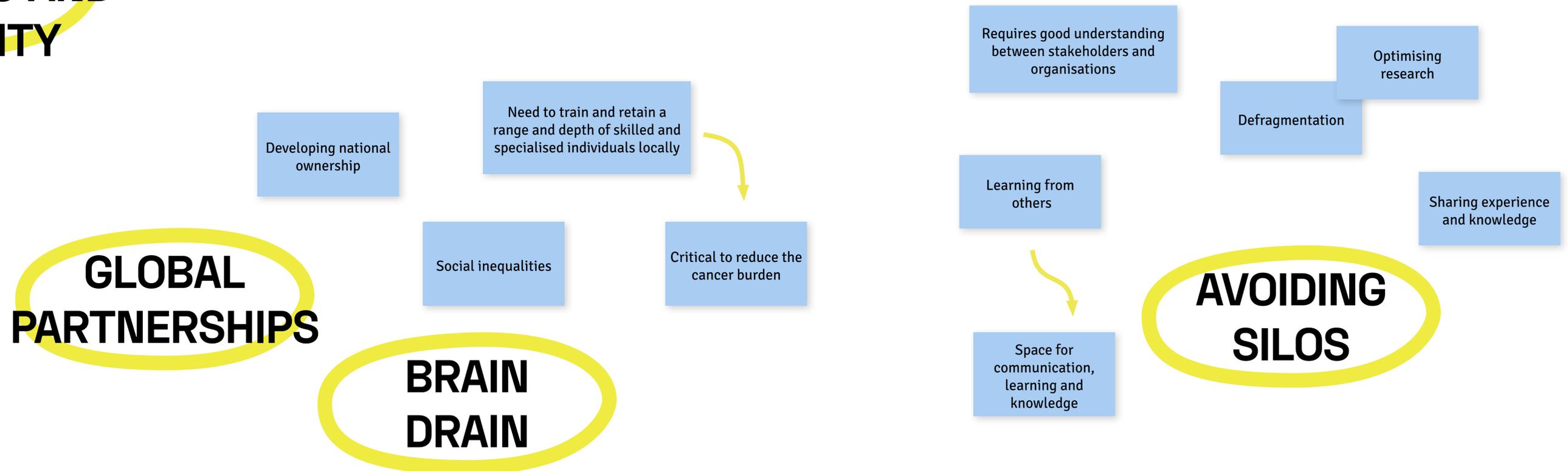
Global partnerships are a critical to reducing the cancer burden. Whilst social inequalities in cancer are recognised in all countries, it is most apparent in low and/or middle-income (LMIC) countries such as Malawi, where it has major effects on the social fabric and the economy. This situation highlights an essential need to train and retain a range and depth of skilled and specialised individuals locally. The loss of local-based skilled individuals to opportunities in more affluent countries is an issue. However, through investment in human capacity and retention of skills and know-how, countries develop national ownership and an ability participate in global partnerships and networks.

‘(international) partnership works based on countries commitment to mutual respect to each other and importance of benefit to both countries’

‘(barriers can be resolved by) training and retaining enough personnel to work in various specialties of our healthcare system. Training is important but also creating an environment that will motivate and retain these trained personnel is crucial. There should be deliberated policies that do not only plan training of personnel but also plan for availability of equipment and facilities’



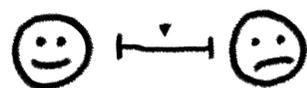
INFORMAL RELATIONS AND CURIOSITY



Learning from treating childhood cancer

Improving outcomes for children and young adults with cancer requires a different model, ethos and approach to clinical trials and the patient. These experiences and ways of working in childhood cancer are of broader relevance to the cancer care community.

QUALITY OF LIFE



Cancer treatments are associated with side effects that can have both short term and long term impacts on a patient's quality of life. Quality of life is highly personal and complex. With increased success in therapies, this aspect of cancer care is critical.

"It does need some innovative ideas about how to fund these things, and how to capture side effects and quality of life information in a rigorous way. These are really important to care for patients. And there's a lot of problems around that. Because quality of life is very, very subjective. Whether life is good or bad is not really easily mapped on to anything objective. And so you can have someone you look at externally who can seem incredibly disabled and have very poor quality of life, who can say, "my life is great", and vice versa, someone who seems to be functioning perfectly well, that says "my quality of life is awful". So learning how to measure that is something we need to think about."

CHANGING POPULATION



Whilst emphasis is often placed on cancer in older age populations, it needs to be remembered that cancer affects all age groups including children. Therefore age may be important in determining care options and in post-cancer life.

"If you are dealing with the average cancer patient who is potentially quite elderly, and you are maybe not necessarily trying to just cure them, but extend their life a little bit, the things you measure are not necessarily the same as would be important to 30 year olds that you are hoping to cure, who then have another 40 years of life ahead of them."

"We're very interested in the side effects of treatment, because obviously, the peak age for childhood leukaemia is age two to five. And, you know, 90% of those children or nearly 93% now have been cured. And, you know, you hope when you cure them, they're going to live to be like 80 or 90 years old. And so, you've got to be very careful not only to cure the leukaemia, but that you haven't done damage to their normal body cells that, okay, might be alright, for 10 years or 20 years, but then might cause problems as they get older. So we have quite a different perspective in that way."



SIDE EFFECTS

Understanding and reducing side effects of treatments is an important yet often underrepresented aspect of cancer research. Side effects impact quality of life and bring a human-centred approach to clinical trial development.

"I think (side effects) are a really, really underappreciated thing by oncologists, and doctors in general. The side effects of treatment are really important to patients. It's probably as important as curing their cancer, the things they have to live with, and I think it's quite easy sometimes as a doctor to see something clinic and say, Alright, I'm going to prescribe you these medicines off, you go home and you don't see what they're having to deal with it at home. And, I think how cancer research is organized at the moment, we're very bad at cataloguing and understanding side effects, that traditional clinical trials way of doing it of filling in these adverse event forms and things. We know from auditing trials, they're incredibly inaccurate. So we both massively overreport, inaccurately report some types of side effects that are easy to measure, like, you know, blood test abnormalities or something and they massively under-report other other areas. And a lot of the time, they are just plain wrong, you know, once side effects are reported and actually we go back to patient notes, it was something different. So our current mechanisms for that are really poor."

Changing dynamics

“We mustn’t forget that this is still very much experimental medicine.”

These are themes we identified referring to changes, currently happening or predicted to happen, that would change the dynamic of trials and the way they are handled.

CHANGING POPULATION

The target population for First in Human Trials is changing, and including less terminal patients who haven’t exhausted their treatment options. This prompts a reconsideration of the side effects and long term effects of treatments.

“Increasingly, early phase trials are open patients who haven’t exhausted their standard treatment options. So then you’ve got a different dynamic, where you need to identify with the people looking after the patient, their primary team, a window of where it is reasonable to look at an experimental treatment, on the basis that they their condition won’t deteriorate, even if that treatment isn’t effective, and that you won’t have exhausted any of your your future treatments. So in breast cancer, we get patients who have reached the end of endocrine therapy, but who don’t have a pressing need to start chemotherapy. That’s an amazing opportunity, in that situation, to look at something that is more novel. So that there has been a move away from these patients being pre-terminal.”



PATIENT INVOLVEMENT IN TRIALS

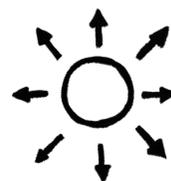
Patients are more willing to take an active role in looking for trials, and trialists understand the need to involve patients and patient representatives at all stages of a trial and its design to better understand their needs.

“So I think there is now that approach, and we get patients hunting for trials. There’s an informed patient population out there.”

“You’ll assume, as a clinician, that a patient wants to reduce number of visits or you know, wants to have tablets, instead of intravenous, or all of the ER make all these assumptions, and you won’t necessarily be right. They may find that coming to the hospital is actually very reassuring and they don’t want to reduce the frequency of visits. Or they may actually hate taking tablets and feel like they’re rattling all day, if they’re having to take 20 tablets a day and prefer to come once every three weeks to have a drip. So, so we can’t assume that we know anything about the treatment pathway without checking the patients.”

“Patients aren’t as involved at the minute as they will be in the future. And I think public and patient involvement is becoming a much more important aspect of research. Having patient input to research decisions, even at an early stage is advantageous even from practical perspectives of the big additional commitment to going on to a phase one trial in terms of hospital visits and extra tests and extra blood tests and biopsies, etc. And, you know, patient representatives from an early stage can let you know what they think might be acceptable and what might not be acceptable, which can help in research and clinical trial planning from an early stage.”

GROWING SCALE



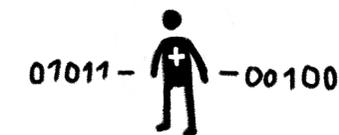
The growing size of Phase one trials disrupts their dynamic and brings a perceived dilution of the unique research opportunities afforded by their small scale.

“(there is a) changing nature of early phase trials. Because we are of a generation that remembers doing phase one trials where there was (...) 20 to 30 patients, but now you’ve got drugs been licensed on the basis of a phase one study where there’s 1000 patients (...) And with that has come perhaps the dilution of the balance between risk benefit and the anticipated benefit for patients as well, the perception has changed. And yeah, we mustn’t forget that this is still very much experimental medicine.”

“Pattern recognition is important, because the way we set up these studies, rather than everybody doing them, you have them concentrated in small number of investigators and small number of centres, so that they see the multiple patients getting treated with the same trial. So they have the opportunity of seeing that unusual, unexpected pattern recognition toxicity that would be diluted if a study of not very large patient sample size was diluted across too many centres.”

“Traditional phase one trialists would say that two or three centres is optimal. And if it’s a tumour specific or site specific trial, you’d say, not a huge number of centres, because it’s not (just) wanting ownership of the patients. If each centre only sees one or two patients, you lose the opportunity for that pattern recognition.”

“If you look at every possible combination of immunotherapy that could be done, there aren’t enough for patients and early phase trials in the world to do it. It is increasingly competitive. But it has to be done in a rational and sensible way.”



DIGITAL DATA & KNOWLEDGE MANAGEMENT

Digital Data collection tools offers new opportunities for monitoring patients and their quality of life more accurately. Available and long-term access to Data streamlines the research process and allows comparison to similar datasets.

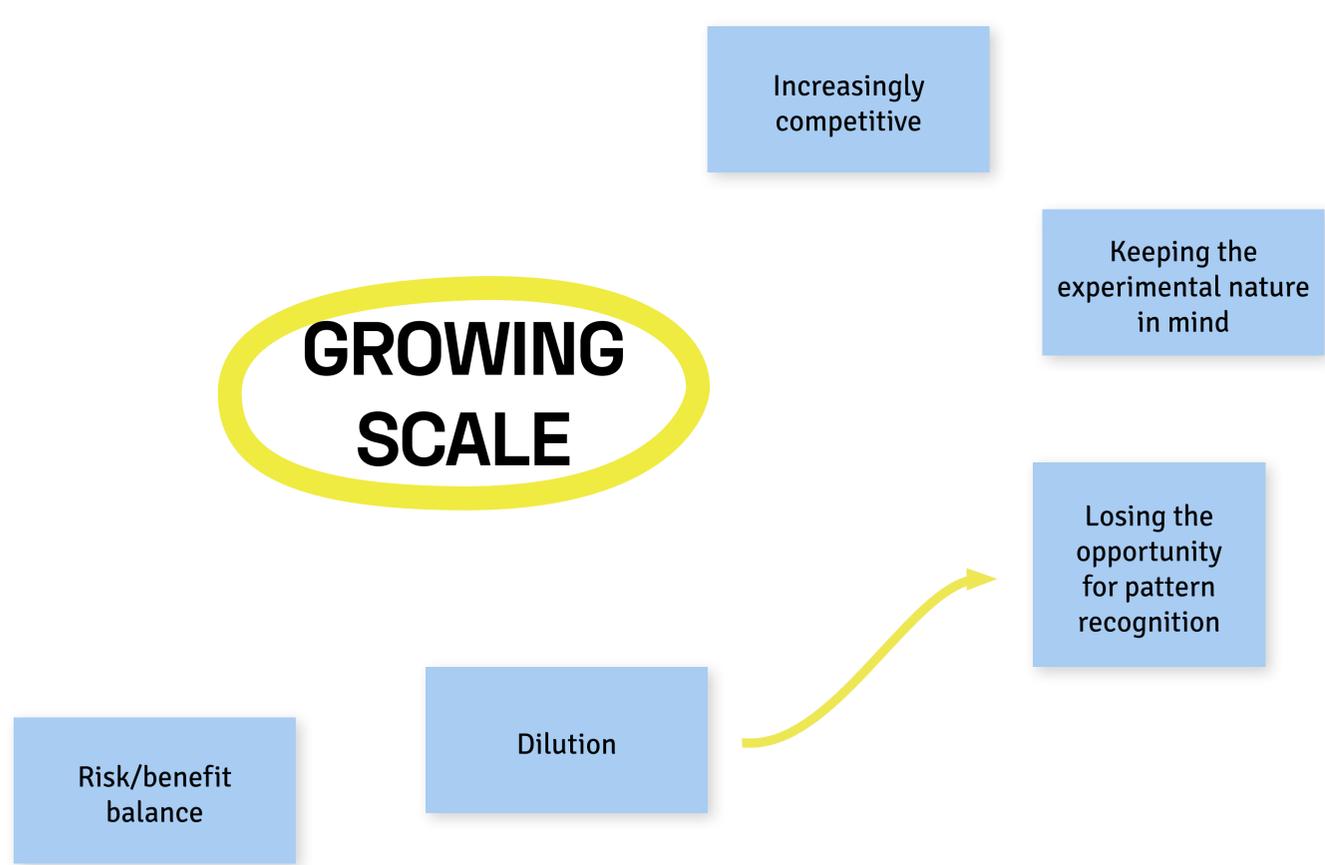
“We’ve been coming through patient reported outcome measures, where you capitalize on digital technology to get patients fill in apps and tell you how they’re feeling and, you know, day by day and collect more real time data.”

“Patients are going to want to do more remotely going forward, I think there will be much more electronic inputting. And I hope that we’ll move away completely from paper data entry. (We will) need to be much more aware of how to do electronic data entry. I’m hoping there’ll be a lot more access to source data so that we won’t have to start from scratch with everybody.”

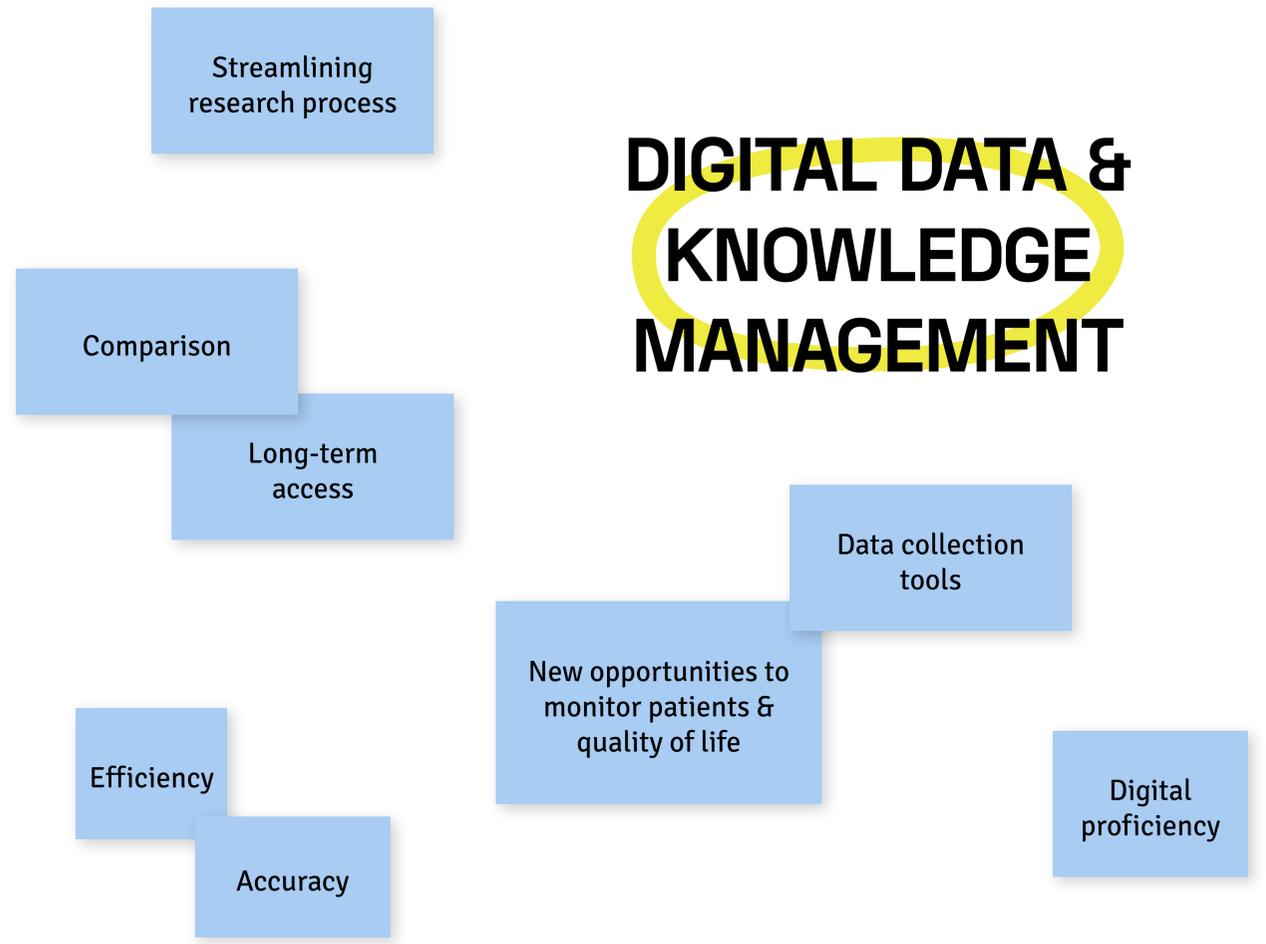
“In our most recent trial, we’ve built in doing a test of brain function, a series of really short computer games, at the end of treatment, the basic tests kind of how well you can concentrate and memorize things and, and kind of plan your way through a maze and things like that. And on its own as a static measurement (...) it might answer a little bit of science, but not loads. But having got that we can then potentially go back and get people to repeat it in five years time. And we’ve got that baseline on all the children.”

“We have this huge potential to be much more efficient in the way we collect data, because the NHS collects a huge quantities of data routinely. And all that data is potentially linkable, collectible and analyzable. And you can use that to return information on trials and make progress. And that’s a massive potential to make things much more efficient.”

GROWING SCALE



DIGITAL DATA & KNOWLEDGE MANAGEMENT

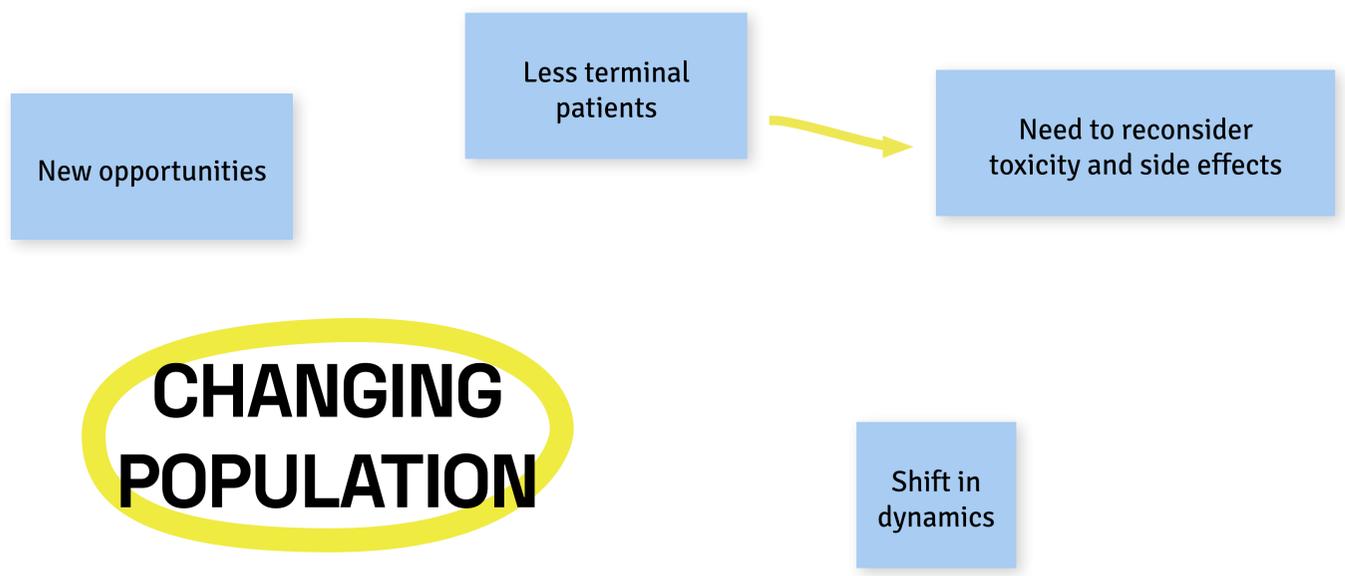


Less terminal patients

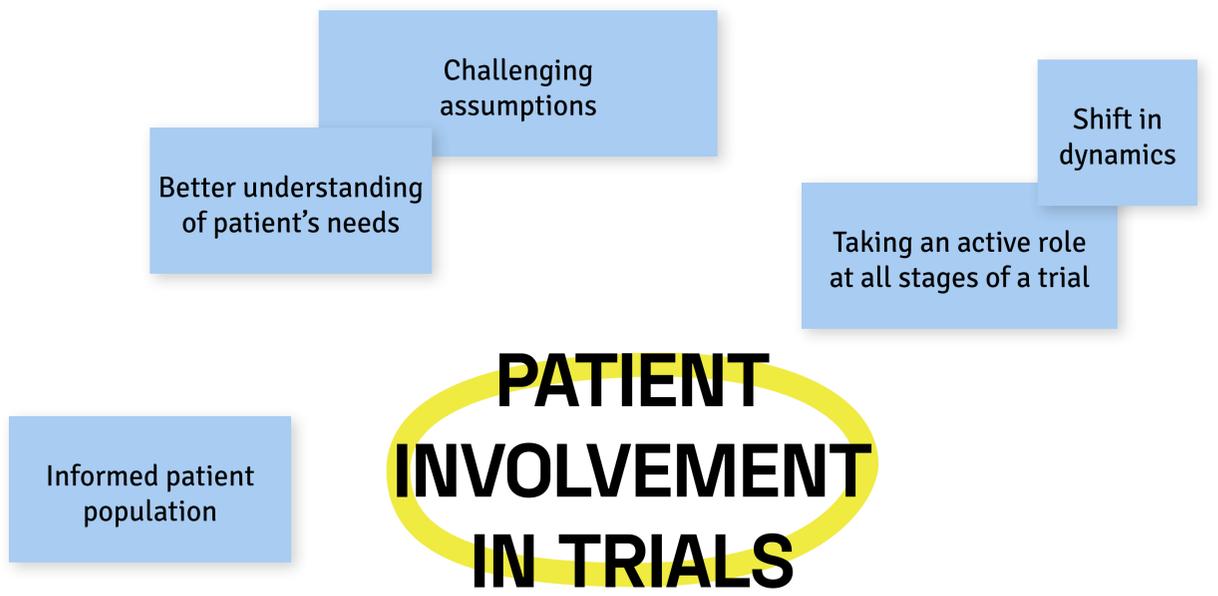
Need to reconsider toxicity and side effects

New opportunities

CHANGING POPULATION



PATIENT INVOLVEMENT IN TRIALS



WHAT'S NEXT?



We reflected on the future population that would take part in phase 1 trials, and the impact early detection and prevention strategies would have on the cancer population. How will the target population for First in Human Trials change in the Future (different tumour types / age groups / disease stage), and what impact will it have on trials? How will Trials have to adapt? For example, if a younger, less terminal population is taking part in Phase 1 trials, how will side effects and long term effects be considered? Will quality of life be measured differently?

COVID-19 has put clinical trials in the public eye and given a very concrete example to show the value of trials. In the future, how can the value of trials be more clearly communicated to promote public awareness?

Trialists will need an increasingly broad knowledge base. How can early career researchers get this experience, and gain more exposure to different types of cancer and treatments?

Phase One Trials currently benefit from the positive dynamics of working in a “niche” subject, with a small scale. What are the positives and what are ways to keep them in the future in a growing field?

Contributors

Peter Gallagher

Queen's University Belfast,
Northern Ireland

Gerard Walls

Queen's University Belfast,
Northern Ireland

Kirsty Taylor

Queen's University Belfast,
Northern Ireland

Rob Jones

University of Glasgow,
Scotland

Shelby Barnett

Newcastle University,
England

Caroline Forde

NHS Greater Glasgow and
Clyde, Scotland

Mark White

University of Glasgow,
Scotland

Sarah Danson

University of Sheffield,
England

Christopher Williams

University of Leeds,
England

Salma El Badri

University of Sheffield,
England

Catherine Hanna

University of Glasgow,
Scotland

Nicol Keith

University of Glasgow,
Scotland

Chris Halsey

University of Glasgow,
Scotland

Bong'eni David Chipole

Kamuzu Central Hospital,
Lilongwe, Republic of Malawi

Jeff Evans

University of Glasgow,
Scotland

Gaston Welisch

University of Glasgow,
Scotland

Christopher Twelves

University of Leeds,
England

Ruth Plummer

Newcastle University,
England

Stefan Symeonides

University of Edinburgh,
Scotland

Booklet and workshop design by Gaston Welisch

<https://gaston.pro/>
gastonwelisch@gmail.com