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Reportage

A risk-based approach to experimental early phase clinical trials during the COVID-19 pandemic

Phase I Drug Development Unit, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, UK (C Tiu, R Shinde, B Rao Baikady, U Banerji, A R Minchom, J S de Bono, J S Lopez)**; and Institute of Cancer Research's Clinical Trials and Statistics Unit, Sutton, UK** (C Yap)
Juanita.Lopez@icr.ac.uk

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Introduction

Experimental cancer medicine has evolved over the past decade, with increasing trial complexity and operational demands. As a dedicated phase 1 trials unit, we are used to change and uncertainty, and exploring new ways to improve our processes. However, the arrival of coronavirus disease 2019 (COVID-19) has caused an upheaval in health-care services. On March 23, 2020, the UK went into lockdown. In this Perspectives piece, we reflect on the extraordinary reshaping of delivery of patient care in our experimental phase 1 cancer clinical trials unit.

Risk–benefit and safety in early clinical trials during the pandemic

Patient safety is the prime objective of early phase trials, which might need to be ranked on the basis of their risk–benefit profile (figure). Drug development clinicians weigh up potential benefit from novel drugs against toxicity risk, while adhering to complex protocols to ensure accurate data collection pertaining to trial-specific endpoints. The weighing of potential benefit against risk is the cornerstone of translation of preclinical discoveries into the clinic, while ensuring compliance with Good Clinical Practice. When initial reports suggested that patients with cancer were at increased risk of COVID-19 morbidity and mortality, it was imperative that they would be shielded to reduce exposure. As one of the largest oncology phase 1 trials unit in Europe, treating more than 300 new patients on nearly 60 actively recruiting trials per year, we had to employ risk management strategies to safeguard patient safety while ensuring integrity of trial conduct. We made the unprecedented, but necessary, decision to temporarily halt recruitment onto cancer clinical trials nationally in light of concerns regarding intensive-care bed availability.

For patients already participating in a phase 1 trial, the first question was whether their net clinical benefit (clinical benefit minus toxicity) was sufficient to expose them to the risk of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) while on an investigational medicinal product (IMP). The second question was how to continue to deliver safe patient care to those continuing on trials while delivering the requirements of trial protocols and ensuring data integrity, following regulatory authority guidance.

Implementation of the risk assessment

At the onset of the lockdown, we had 98 patients on investigational trials, with a further 29 in screening before commencement. We held discussions about the change in the risk–benefit balance of pursuing an experimental trial with patients. 34 (35%) of 98 patients were deriving a clear clinical benefit without substantial toxic effects and had received more than four courses of treatment (at least 12 weeks), so they continued on trial. Six patients considered to be benefiting on trial were deemed to be at higher risk of morbidity should they contract SARS-CoV-2 and had IMP interrupted (two due to previous pneumonitis; four due to reduced respiratory reserve [three with lung cancer, one with mesothelioma]); the intent was to restart IMP once the risk–benefit balance improved.

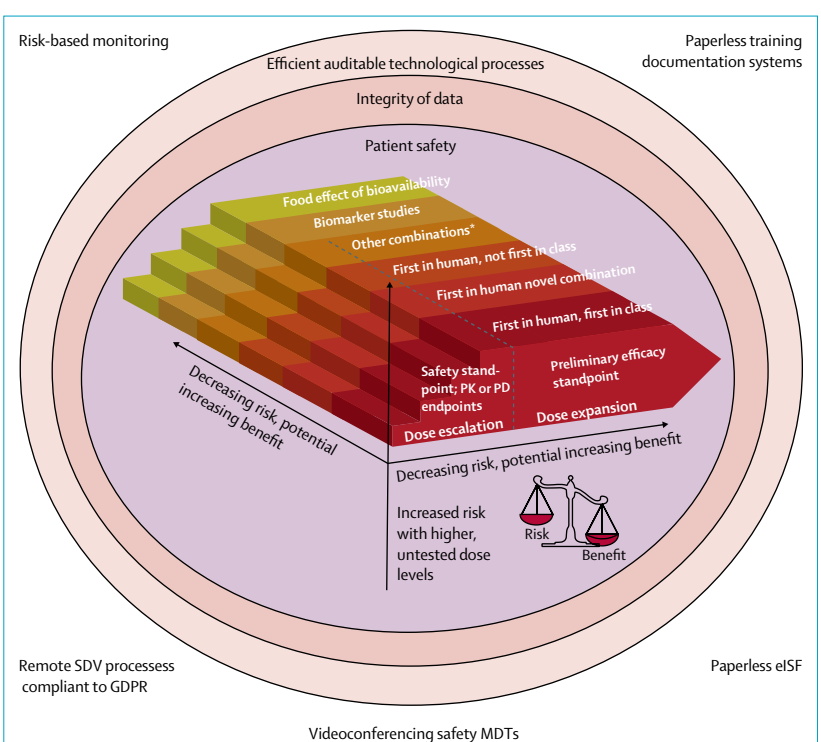

Figure: **Model for a nuanced risk-based approach to early phase clinical trials**
eISF=electronic Investigator Site File. GDPR=general data protection regulation. MDT=multidisciplinary meeting. PD=pharmacodynamic. PK=pharmacokinetic. SDV= source data verification. Three-dimensional figure illustrates relative risk of different phase 1 trials. The risk of each trial reduces as trials progress from escalation into expansion, and with increasing familiarity with a drug or class of drug. A completely novel drug or a completely novel combination carries the highest putative risk (first-in-human or first-in-class). Novel drugs belonging to a class of drugs already studied in humans, or a combination of new and approved drugs, or combinations of drugs belonging to classes of drugs already safely combined with important clinical antitumour activity, have moderate risk. Food-effect studies, drug–drug interaction studies, the testing of new formulations of a drug, or testing in a specific population (eg, patients with renal or hepatic impairment) are much lower risk. Additionally, for each patient, their personal risk reduces with increasing time on trial. The relative intensity of onerous in-person assessments and monitoring could be safely tailored in an adaptive manner depending on the risk-benefit assessment. *Drug combinations that are not first-in-human.

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For more on the **risks of COVID-19 for patients with cancer** see *Lancet Oncol* 2020; **21:** 335–37

For more on **regulatory authority guidance for COVID-19** see https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19, and https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Of the 58 patients within the first 12 weeks of trial, four (7%) withdrew consent due to COVID-19 concerns, 36 (62%) were discontinued from trial participation because of a deemed lack of clear benefit (progressive disease or stable disease with increasing size of target lesions). Only 16 (28%) of 58 patients continued on trial, with both clinicians and the patients agreeing that the risk–benefit balance merited this.

Of the 29 patients in screening, 15 (52%) patients did not proceed to trial participation because of patient anxiety about the risks of COVID-19 or were assessed by their clinician as high risk to proceed. Four patients could not commence trial because of a lack of support services for mandatory screening biopsies. Of the nine patients who did proceed, seven were on expansion trials in which a possibility of clinical benefit was envisioned. One patient had passed screening and was planned to commence an untested dose level of a novel drug, but was moved to a previously cleared dose cohort following sponsor discussion.

All patients who had elected to participate or continue on study within their dose-limiting toxicity (DLT) reporting period had all trial-related assessments done per protocol, ensuring collection of crucial safety parameters. Patients outside the DLT period but within first 12 weeks of trial were overseen by a combination of monitoring by telephone and in-person hospital visits, depending on adverse events and IMP tolerance and including delivery of protocol-specified trial endpoint assessments (pharmacokinetic or pharmacodynamic sampling and imaging assessments). Patients who had received four or more courses of treatment were monitored by telephone (including documenting and grading of adverse events and concomitant medications), with an in-person visit offered if symptoms changed. Those on oral IMP were dispensed two courses, which could be couriered if needed, whereas those receiving intravenous IMP attended unaccompanied on days of IMP administration (having been screened for COVID-19 symptoms over the telephone the day before).

Clinical trial data integrity

As recommended by the UK Medicines and Healthcare products Regulatory Agency, communication between site and sponsor ensured clear documentation of contingency measures. We held our weekly safety multidisciplinary meeting online, and continued to discuss all trials and patients; urgent safety updates and training pertaining to COVID-19 enabled continued oversight. We instituted weekly operational team virtual meetings to oversee major procedural changes. When the timely obtaining of wet-ink signatures was no longer possible, email confirmation from a verified institutional account was deemed acceptable.

Accurate collection, collation, and transcription of clinical data remained a priority; remote access to electronic health records and the use of video conferencing enabled the continuation of data entry and query resolution in a timely manner by staff working off-site. We pursued options for remote source data verification and source data review, including emailing de-identified source documents or screen sharing them using videoconferencing, prioritising the monitoring of patients within the DLT period or those with notable drug-induced adverse events, and the monitoring of other crucial data pertaining to trial-specific endpoints.

Horizon scanning

COVID-19 is unlikely to be eradicated soon, and social distancing and shielding will probably remain necessary for some time. As we plan a resumption of clinical trial activity, we can speculate on how procedures will evolve; the post-COVID-19 clinical trials landscape will most likely look quite different to the one which preceded the pandemic. Risk management in early phase trials has always been necessary. Higher risk phase 1 trials such as first-in-human, first-in-human combinations, and all dose-finding studies, should be done in dedicated drug development units (figure). The high frequency of in-person visits, safety monitoring, and investigator oversight is crucial to safeguard patients.

The number of new cases of COVID-19 in our hospital is low, and decreasing. We adopted testing of symptomatic staff early, with notification of workplace contacts, and weekly testing of all asymptomatic staff has now been introduced. All patient-facing staff and patients are required to wear disposable surgical masks in clinical areas. Patients will be tested for COVID-19 at time of consent and confirmed negative before coming into the unit for screening procedures (oral swabs). Testing will be repeated weekly. Any patient who tests positive for COVID-19 before commencing IMP will have to defer starting on trial until confimed asymptomatic with repeated negative swabs. IMP administration will be halted if a patient is symptomatic or tests positive for COVID-19, until viral tests are negative and the patient is asymptomatic. By keeping our drug development unit as COVID-19-free as possible, we hope to reduce the risk of patients being non-evaluable or having additional adverse events.

As familiarity with a novel drug increases, and with establishment of safe dose and transition to expansion phases, it might be possible to introduce a more nuanced approach while ensuring accurate data. As experience increases with second-generation and third-generation drugs targeting similar pathways, these phase 1 trials might be considered lower in risk and suitable for a less intense schedule. This adaptive approach might include reducing the frequency of in-person visits, using remote

monitoring (either by teleconferencing, shared care with local providers, or electronic patient-reported outcome tools). Patients who remain on trial beyond 12–24 weeks with clinical benefit and no safety concerns should be permitted to reduce the frequency of in-person visits. Patients have responded positively to these risk-based changes; we must now endeavour to maintain their safety and quality of life as the pandemic recedes. The lessons we have learnt during the COVID-19 outbreak need to be evaluated and potentially incorporated into new operating procedures and protocols.

A risk-based approach to operational management is an established standard in early clinical trials. However, need being the mother of invention, the COVID-19 pandemic might result in new ways to increase efficiency, reduce trial costs, and, possibly accelerate drug development. A focused risk-monitoring strategy has been advocated by others, and is reported as increasing productivity and making efficiency savings of up to 20%. Investments in digital infrastructure will propel us towards a paperless future, with electronic site files and training documentation workflows that can simplify work processes, ensuring a robust audit trail.

The changes required in response to the restrictions imposed by the COVID-19 pandemic have, in effect, telescoped the future. Trends that might have taken years to play out have unfolded in weeks. We must embrace these changes, ensuring that we continue to improve the early clinical trials process.

Fore more on **UK recommendations for COVID-19** see *Lancet Oncol* 2020; **21:** 624–27

For more on **risk-monitoring strategies** see http://www.appliedclinicaltrialsonline.com/risking-it-all-going-all-rbm-adoption

Crescens Tiu†, *Rajiv Shinde*†, *Christina Yap*, *Bindumalini Rao Baikady*, *Udai Banerji*, *Anna R Minchom*, *Johann S de Bono*, **Juanita S Lopez*

†Contributed equally

Digital Oncology

Digital tools for sharing genetic information with family members

When a disease-causing genetic variant is identified in an individual, communicating this information to family members can have an essential role in the early diagnosis of relatives. However, evidence suggests that many at-risk relatives are never informed. Ideally, patients communicate directly with relatives, but distant or difficult family relations can become barriers to communication. Patients might also be concerned that sharing information will cause distress or harm to family members, for instance because of genetic discrimination (ie, treating an individual or a group unjustly or prejudicially on the basis of their genetic characteristics, for example, for insurance or employment purposes). Current standard practice recommends clinicians provide a written letter informing relatives about their genetic risk and encouraging them to seek testing. Family communication is important when a condition is severe and actionable. In the case of hereditary cancers, communication is particularly important because it enables early diagnosis, prevention, and treatment. This family letter is distributed either by the patient or by the clinician at the patient's request. These letters might help initiate communication between relatives. However, it is unlikely that they can replace verbal communication entirely and their efficacy is limited, particularly when there are strained family relations. Furthermore, it does little to address other communication barriers.

In response to these pitfalls, several digital tools have been developed to reduce the burdens of communication. FamGenix is a privately developed app released in November, 2019, that enables users to share genetic information with relatives, including autogenerated pedigrees created by genetic risk algorithms. Other examples of digital tools for this purpose include Kintalk and Family Web. These digital tools are being touted as a way to substantially improve preventative health care by facilitating family communication of genetic information. But is this justified? And what new concerns could they present?

Digital tools have the potential to lessen the practical barriers of family communication. They might help to identify at-risk individuals with the use of genetic risk prediction algorithms. For example, FamGenix predicts hereditary cancer risk using the algorithms Gail, Claus, and BOADICEA. Users can decide whether they will discuss the findings with relatives and share them via text or email. By using the app, relatives can add their health information to update the family pedigree and to recalculate genetic risk.

Center for Biomedical Ethics and Law, Department of Public Health and Primary Care (A Phillips, P Borry), **and Life Sciences and Society Lab, Center for Sociological Research, Faculty of Social Sciences** (I Van Hoyweghen, J Kuiper), **KU Leuven, Leuven, Belgium; Melbourne Law School, University of Melbourne, Parkville, VIC, Australia** (D F Vears); **and Murdoch Children's Research Institute, Parkville, VIC, Australia** (D F Vears)
amicia.phillips@kuleuven.be

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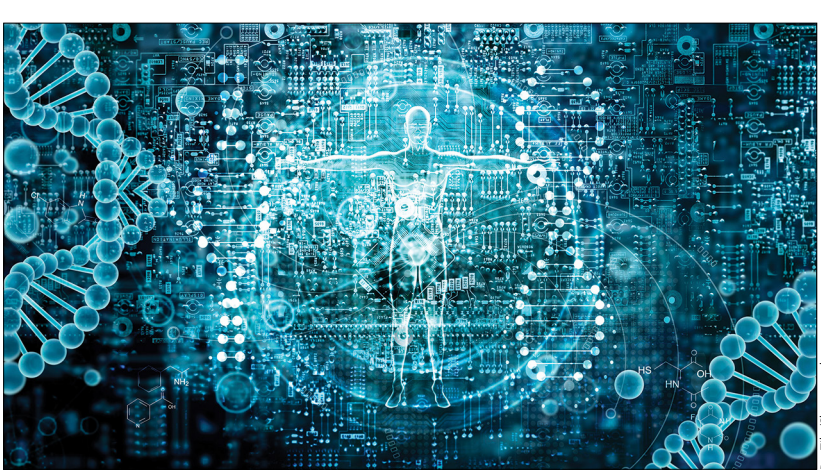

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