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

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Introduction

Experimental cancer medicine has evolved over the last decade with increasing trial complexity and operational demands.[1] As a dedicated Phase I trials unit, we are used to change and uncertainty and exploring new ways to improve our processes. And then COVID-19 arrived; causing upheaval in healthcare services. On the 23rd of March 2020, the United Kingdom went into lockdown. In this perspective piece, we reflect on the extraordinary reshaping of delivery of patient care on experimental Phase I cancer clinical trials.

Risk-benefit and safety on early clinical trials during the pandemic

Phase I trials may need to be ranked contingent on risk/benefit **(Figure 1).** Patient safety is the prime objective of early phase trials. Drug development clinicians weigh up potential benefit from novel agents against toxicity risk, while adhering to complex protocols to ensure accurate data collection pertaining to trial-specific endpoints. This is the cornerstone of translation of preclinical discoveries into the clinic whilst ensuring compliance with Good Clinical Practice. When initial reports suggested that patients with cancer were at increased risk of COVID-19 morbidity and mortality [2] , it was imperative that they be shielded to reduce exposure. As one of the largest oncology phase 1 trials unit in Europe treating 300+ new patients on nearly 60 actively recruiting trials a year, we had to employ risk management strategies to safeguard patient safety while ensuring integrity of trial conduct. An unprecedented but necessary decision was made 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 I trial, the first question was whether their net clinical benefit (clinical benefit minus toxicity) was sufficient to expose them to the risk of acquiring COVID-19 whilst on an experimental agent. 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.[3, 4]

Implementation of the risk assessment

At the onset of the lockdown, we had 98 patients on investigational trials, with a further 29 in screening prior to commencing . Discussions of the change in the risk-benefit of pursuing

an experimental trial were held with patients. Thirty-four patients (35%) were deriving clear clinical benefit without significant toxicity, and had received more than 4-courses of treatment (at least 12 weeks) - these continued on trial. Six patients considered to be benefiting on trial were deemed to be at higher risk of morbidity should they contract COVID-19 and had investigational medicinal product (IMP) interrupted (2 with prior pneumonitis; 4 with reduced respiratory reserve – 3 lung cancer, 1 mesothelioma); the intent was to restart IMP once the risk-benefit balance improved.

Of the patients within first 12-weeks of trial, 7% (4/58 patients) withdrew consent due to COVID19 concerns, 62% (36/58 patients) were discontinued from trial participation due to a deemed lack of clear benefit (progressive disease, or stable disease with increasing size of target lesions); Only 28% (16/58 patients) continued on trial with both clinicians and the patients deeming the risk benefit balance merited this.

Of the 29 patients in screening, 15 patients (52%) did not proceed to trial participation due to patient anxiety about the risks of COVID-19; or as assessed by clinician as high risk to proceed. Four patients could not commence trial due to lack of support services for mandatory screening biopsies . Of the 9 patients who did proceed, 7 of these were on expansion trials where it was envisioned there was a possibility of clinical benefit. One patient had passed screening and was planned to commence an untested dose level of a novel drug was moved to a previously cleared dose cohort following sponsor discussion.

All patients who had elected to participate, or continue, on trial within their dose-limiting toxicity reporting (DLT) period had trial related assessment carried out per protocol ensuring collection of critical safety parameters. Patients outside the DLT period but within first 12-weeks of trial were overseen by a combination of telephonic monitoring interspaced with in-person hospital visits depending on toxicities and IMP tolerance; including delivery of protocol-specified trial endpoint assessments (PK or PD sampling and imaging assessments). Patients having received 4 courses or more of treatment were monitored telephonically (including documenting and grading adverse events and concomitant medications), with an in-person visit offered if change in symptomatology. Those on oral IMP were dispensed two-courses which could be couriered if needed, while those on intravenous IMP attended

unaccompanied on days of IMP administration (having been screened for COVID-19 symptoms over the phone a day prior).

Clinical trial data integrity

As recommended by the UK regulatory authorities[6], the MHRA, communication between site and sponsor ensured clear documentation of contingency measures. Our weekly safety multi-disciplinary meeting was conducted online and continued to discuss all trials and patients; urgent safety updates and training pertaining to COVID-19 enabled continued oversight. Weekly operational team virtual meetings were instituted 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. Options for remote source data verification and source data review were pursued, including emailing de-identified source documents or screen sharing these using videoconferencing with study monitors. Prioritization of monitoring of patients within DLT period, with significant drug-induced toxicities and of data pertaining to trial-specific endpoints was made.

Horizon scanning

COVID-19 is unlikely to be eradicated soon; social distancing and shielding is likely to remain necessary. As we plan a resumption of clinical trial activity, we can speculate on how procedures will evolve; it is likely that the post-COVID clinical trials landscape will look quite different to that thatwhich preceded the pandemic. Risk management in early phase trials has always been necessary. Higher risk Phase I trials such as first-in-human and first-in-human combinations and all dose-finding studies should be carried out in dedicated drug development units **(red-orange bars in Figure 1).** The intense frequency of in-person visits, safety monitoring, and investigator oversight is critical for safeguarding patients .

The number of new cases of COVID19 in our hospital is low and falling. Testing of symptomatic staff was adopted early, with notification of workplace contacts. Weekly testing

of all asymptomatic staff has now been introduced. All patient-facing staff and patients have been required to wear disposable surgical masks in clinical areas. Patients will be tested at time of consent and confirmed negative prior to coming into the unit for screening procedures. Testing will be repeated weekly. Any patients that are positive prior to commencing IMP will be deemed screen-failures and considered for rescreening once symptoms have resolved and tested negative. IMP administration will be halted if patients are symptomatic or Covid-swab positive until viral tests are negative and asymptomatic. By keeping our drug development unit as COVID-free as possible, we hope to reduce the risk of patients experiencing increasing toxicity or being non-evaluable.

As familiarity with a novel agent increases, and with establishment of a safe dose and transition to expansion phases, it may be possible to introduce a more nuanced approach whilst ensuring accurate data. As experience increases with second- and third-generation agents targeting similar pathways, these Phase I trials can possibly be considered lower in risk and suitable for a less intense schedule. This adaptive approach may include reducing intensity of in-person visits, utilising remote monitoring – either by teleconferencing, shared care with local providers, or electronic patient reported outcome (ePRO) tools. Patients who remain on trial beyond 12-24 weeks with clinical benefit and no safety concerns should be permitted to scale down the intensity of in-person reviews. 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 COVID-19 need to be evaluated and potentially incorporated into new operating procedures and protocols.

In conclusion, risk-based approaches to operational management of trials is an established standard in early clinical trial conduct. However, necessity being ‘the mother of invention’, the COVID pandemic may result in new ways to increase efficiency, reduce trial costs and, possibly, accelerate drug development. A focussed risk-monitoring strategy has been advocated by others, and reported as increasing productivity and up to 20% efficiency savings in monitoring .[5] 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, ensuring we continue to improve the early clinical trials process.

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Figure legend

Figure 1 Model for a nuanced risk-based approach to early phase clinical trials. 3D figure illustrates relative risk of different Phase I trials.

A completely novel agent, or a completely novel combination carries the highest putative risk (first in human/ first in class) **(red/orange bars**). Novel agents belonging to a class of drugs already studied in humans, or a combination of new and approved drugs or combinations of agents belonging to classes of drugs already safely combined with important clinical antitumour activity has moderate risk **(brown/gold bars**). Food effect studies, drug-drug interaction studies, the testing of new formulations of a drug or testing in specific population, eg patients with renal or hepatic impairment are much lower risk **(light yellow bars**). The risk on each trial reduces as trials progress from escalation into expansion (right axis); and with

increasing familiarity with agent/class (left axis). Additionally, for each patient, their personal risk reduces with increasing time on trial. The relative intensity of onerous in person assessments as well as monitoring could be safely tailored in an adaptive manner depending on the risk/benefit assessment.

Figure 1 Risk Based Approach to Phase I clinical trials