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Litigation Over Clinical Trials - The Importance of Causation

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In a recent judgment in *Cardiorentis AG v Iqvia Limited and Anor [2022] EWHC 250 (Comm),* the English Commercial Court examined in detail, for the first time in the United Kingdom, the duties and standards required of contract research organisations in clinical trials.

BACKGROUND

The case involved a claimant drug-development-company specialising in exploring treatments for heart failure and cardiovascular diseases, and a defendant contract-research-organisation (CRO) providing clinical trials services. The Court looked at the contractual arrangements for, and the conduct and results of, a phase III clinical trial to investigate the efficacy and safety of a drug named "Ularitide" in patients with acute heart failure.

The claimant had been investigating the potential benefits of Ularitide for over 20 years, through phase I and II clinical trials during the 1990s and 2000s. After those trials showed promise, the claimant engaged the defendant CRO to provide clinical trial services for a phase III trial, which took place during 2012 to 2015.

Unfortunately, the trial did not yield sufficiently positive results and was unable to indicate improved patient outcomes in those receiving the drug treatment. The claimant subsequently alleged that the defendant had, among other things, failed to: adequately train the clinical trial investigators and medical advisors involved in the study; monitor the trial sites and adequately identify deviations from the clinical trial protocol; take steps to prevent or remedy protocol deviations; report protocol deviations to the claimant promptly or appropriately; and adequately verify the accuracy of data entered into the clinical trial database.

In particular, the claimant claimed that irregularities at certain testing sites led to ineligible patients being enrolled into the clinical trial and the defendant had not reported or rectified those irregularities adequately or at all. Consequently, the claimant contended that: the clinical trial was not capable of providing reliable phase III data on the efficacy of the drug; the results of the trial were of little practical or scientific value; it had been deprived of the opportunity to earn revenue on the development of the drug; and the money spent on the trial had been wasted because it could not be used reliably for submission to regulatory authorities to seek marketing approval.

The claimant also sought access to the clinical trial data - which had been withheld by the defendant

pending payment of outstanding invoices for its clinical trial services, in respect of which the defendant counterclaimed.

COURT'S FINDINGS:

- The Court recognised that, in engaging a CRO to provide clinical trial services, a trial sponsor (the claimant in this case) is not contracting for the conduct of a study which would produce a particular result. It is contracting for the conduct of a study which produces a meaningful and interpretable result, whether positive or negative, as far as the efficacy of the drug is concerned.

- The contractual standard to which the services were to be provided in this case (being those customary in the CRO industry) was no lower than the standard of reasonable skill and care implied by the Supply of Goods and Services Act 1982.

- There is surprisingly limited data available on usual or expected levels of patient eligibility deviations in clinical trials, and the nature of the studies themselves will be fact-specific in any event. For example, a study of an acute condition, where a decision on patient enrolment needs to be taken quickly in an emergency situation, is likely to produce a higher level of eligibility deviations when compared with a study of a chronic condition where eligibility decisions can be taken more deliberately.

- Some protocol deviations (including eligibility deviations) are to be expected in most clinical trials, albeit there is no recognised threshold or benchmark for the number or percentage of eligibility or other protocol deviations which would mean that drug regulators or the scientific community would consider such a study to be unreliable.

- Clinical trial investigators make mistakes from time to time when conducting a trial of this nature in the pressured environment of an emergency setting.

- The existence and number of eligibility violations alone does not constitute a red flag as to whether the study was conducted competently, or whether it would be accepted as an interpretable study by regulators or the wider scientific community.

- Drug regulators would not look simply at the number of patient eligibility deviations, but would evaluate the extent to which those deviations affected (or not) the reliability of the efficacy or safety data from the clinical trial.

- In a Food and Drug Administration (FDA) clinical review of a previous trial of a similar heart failure treatment, the incidence of protocol deviations were similar to the deviations in this case. In that clinical review, the FDA concluded that the majority of the protocol deviations (including patient eligibility deviations) had not affected the trial's efficacy or safety findings, nor was there any evidence that the trial was regarded as having been poorly performed as a consequence.

- The claimant had not proved that the training of the medical professionals conducting the trial or the clinical research associates liaising with the trial sites, was inadequate. The number of eligibility violations alone did not evidence a failure in monitoring or data verification. What occurred was not out of the ordinary and, in general terms, the defendant had acted and reacted reasonably. Accordingly, the claimant did not succeed in showing that patient

eligibility or other protocol deviations were the result of a breach of contract.

- Whilst there was some delay by the defendant in dealing with and reporting protocol deviations once identified - and there may have been breaches of the parties' contracts in relation to those matters - they had very little causative effect.

- Notwithstanding the protocol deviations, the trial was a robust and interpretable study, albeit one which did not indicate improved patient outcomes. It had been undertaken conscientiously by those involved on both sides and represented a professional attempt to identify an appropriate set of patients and results. It was not the enrolment of ineligible patients which led to the study being negative, it was because the results accurately reflected the effect of the drug treatment on the population involved for the endpoints being examined. Even if there had been no breach or the ineligible patients had been omitted, the clinical trial would still have produced a negative result overall.

- The results were such as to have satisfied the scientific community as to the effectiveness or otherwise of the drug in relation to the endpoints examined, and therefore the expenditure on the clinical trial cannot be said to have been wasted. Even if it could be said that there were failures by the defendant, and that those failures had some effect in making the results of the study less favourable to the drug treatment than they would otherwise have been, the failures cannot realistically have made sufficient difference to the prospects of achieving regulatory approval.

- The claimant's claim to access the data and information generated by the trial succeeded. Whilst the defendant does not have to deliver it up unless and until it has been paid in full under the parties' contracts, nothing in those contracts entitles the defendant to deny the claimant access to the data, and the claimant is under a regulatory obligation (under the Medicines for Human Use (Clinical Trials) Regulations 2004) to keep a master data file and ensure that it is readily available at all reasonable times by the relevant licensing authority or by any person appointed to audit the arrangements for the trial.

- The defendant's counterclaim also succeeded, and the claimant was ordered to pay the defendant €4.5 million in respect of unpaid invoices for services provided in connection with the clinical trial.

COMMENT

Ultimately, the Court held that the clinical trial produced reliable and interpretable data. Whilst there had been some mistakes, they did not affect the overall integrity of the data and could not be said to have caused the claimant loss. Had there been no mistakes, the claimant would still have been in the same position; with a phase III clinical trial which unfortunately did not indicate improved patient outcomes.

The decision is illustrative of the importance of (and potential difficulties in) proving causation in disputes of this nature. Clinical trials involve very significant investment of time and resources, and the prize of a successful phase III trial which could lead through to a successful application for regulatory approval to market the drug, can be very significant. So too, therefore, could be the damage caused to a clinical trial sponsor in circumstances where the development of an efficacious, safe, and marketable drug is hindered or delayed by problems or mistakes in conducting clinical

trials. Competing drugs may win a race to market, contractual milestone payments may be missed, the future financial viability of a drug may be prejudiced, and the trial sponsor may lose the opportunity to maximise potential revenues from the exploitation of the drug.

As the Court identified in this case, there will always be some mistakes and protocol deviations in complex clinical trial settings, although they will not necessarily constitute a breach of duty / standard of care (subject to the facts of a case and the contractual terms). Even if they do, the breach may not have any causative effect on the outcome of the clinical trial and the viability of the drug for commercial exploitation. However, a breach which does have a causative effect on the failure of a clinical trial or a delay or failure in securing regulatory approval to market an efficacious and safe drug, could result in a significantly different outcome.

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