Entering a clinical trial: consent and contract – a consideration

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Abstract

Whether Phase I healthy volunteer research has a contractual nature has been doubted by some given that the consent process that governs such research emphasizes that the subjects are completely free to withdraw at any stage. Certainly, in practice, such volunteers are immune from any contractual obligations because of their overriding right to withdraw at any time. Here though it is made very clear that nevertheless a contract does arise, and it may have some interesting implications in particular research situations. The contemporary position is brought into focus by outlining the history of the use of the term 'contract' in such studies, and certain related legal concepts are also explored which should be helpful information for those (such as members of ethics committees) required to consider protocol amendments or the arrangements for prorated payments.

"I'm a[n]…attorney…I draw up contracts for my clients. Contracts that have no loopholes, except in their favour."

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Whilst both contract law and legal issues concerning informed consent have an extensive bibliography associated with them, very little has been written addressing their conjunction. The present paper aim to clarify that lacuna, as few writers go further than merely acknowledging an uncertainty:

"Whether researchers and subjects enter into a contract as a result of the consent process has been a matter of some question."

Here I shall argue that invariably when healthy volunteers (I do not talk about trials where patients are involved because in such circumstances they may have the prospect of a therapeutic benefit) give their consent to engage in a clinical or other medical trial, by doing so, they also tend to enter into a contract. This applies notwithstanding the fact that the subject, under virtually all ethics guidelines that govern human subjects research, is freely able to withdraw from the study at any time and without any penalty. An insight into this area of the law is presented here as useful for members of research ethics committees - especially perhaps for those who come across the explicit use of the term 'contract' in the consent forms - and also for researchers to better understand their obligations, and for subjects to better know their rights. Although it is important to note that it is English law which is concentrated on, similar issues apply in many other modern law jurisdictions and so the concepts (if not always the precise legal approaches) discussed can still illustrate the contractual underpinnings.

Perhaps the difficulty that has caused the question which Glantz refers to centres on the virtually obligatory phrase which has already been alluded to, and which is invariably introduced into the consent process (and its documentation), which gives one party (the 'subject' in our example) the freedom to withdraw (or 'opt out' of the contract) at any stage without penalty. If a contract has been formed out of the consent process, such a clause seems to laugh in its face. As shall be seen, any resultant contract certainly becomes a bit unhinged around this clause, but the contract does not quite dissolve and it remains, if seriously wounded, latent and capable of acting where circumstances permit. The withdrawal clause can be seen as a truly marvellous loophole for the subject, which would allow them to run rings around contract lawyers – and perhaps goes some way to account for the lack of case law on the topic. However, it shall be suggested that use of the term 'contract' might have a psychological effect on the subject, which may have benefits for the other party although whether this may be why indeed some companies or their researchers occasionally still explicitly use the term in their consenting documentation is doubted. Rather this paper intends to gather the facts about contract law and discuss them in the context of healthy

volunteer trials – as this has, as Glantz has pointed out 'been a matter of some question'.[2]

Throughout I shall have occasion to question how the contract would act were it not for the 'opt out' clause. Such a contract as I have in mind tends to arise naturally because of the conjunction of the elements needed for consent (as I shall shortly discuss) together with the fact of consideration. Such a conjunction invariably arises in the case of healthy volunteer studies such as Phase I research – but not so frequently where patients are involved - and thus it shall be these studies that shall be the focus of this paper. A little history will help give some context to the discussion as contracts governed the research relationship before the notion of informed consent took over.

REED'S YELLOW FEVER EXPERIMENTS

When Walter Reed famously used human volunteers for his yellow fever experiments, he was careful that his engagement of such subjects avoided the censure that had surrounded Giuseppe Sanarelli after the latter claimed to have isolated the agent involved in yellow fever. Sanarelli had boasted that he had successfully induced yellow fever in five people by infecting them with the causative agent, an action which Sir William Osler condemned: "To deliberately inject a poison of known high degree of virulency into a human being unless you obtain that man's sanction, is…criminal." Reed sought to avoid such opprobrium and introduced a five-fold protective envelope around his research in an attempt to preclude possible claims of any immorality. Firstly, he ensured a degree of auto-experimentation with the researchers also acting as participants. Secondly, only adults were accepted as participants. Thirdly, those participants would be required to sign written contracts. Fourthly, there would be financial payment to the participants and fifthly, the written contract contained a clear declaration of consent.

Reed's contract was available in both English and Spanish, and highlighted the risks involved:

"The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent."

Usually when Reed's experiments are discussed, it is in connection with the development of the concept of consent. Here though I want to use his experiments as a vehicle to explore the potentially contractual nature of human participant research.

DISUSE OF THE TERM 'CONTRACT'

Informed consent (undue influence and therapeutic misconception notwithstanding) was not a fully articulated concept at the time of Reed's work. Indeed the term 'contract' was used until there arose a much greater development of the understanding of 'informed consent' which came in the 1950s and especially in the 1960s: what we now know as "written consent forms ([were] then usually called contracts, releases or waivers)." This latter point emphasizes perhaps that such documents were used more to protect the researchers than to protect or help inform the participants. Capron certainly speculates that the term 'contract' in human experiments may have served to relieve the researcher of any liability when proceeding with what might have become unjustified research.

It has been suggested that if written consent was obtained there would be no value in going on to refer to the contractual nature of the arrangement, with its unpleasant and contextually inappropriate overtones of legalese, rather than the medical care that might be more appropriately emphasized. The term 'contract' might however perhaps seem a more appropriate term to some in that it may serve to distance the researcher and their subjects (especially in later phases of research where the subject will also be a patient) by emphasizing to the latter in particular that what they are engaged in is research, and the care they may be getting is perhaps really more like 'customer service' than patient care. However, when the subject is a patient, there is the hope of medical benefits and consent to treatment governs the relationship, rather than contract law.

One development in the notion of informed consent which may also have contributed to a deemphasizing of the contractual nature of much that is consent, has been that it became forbidden to temper any consent by the use of "any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents for liability for negligence" (45 CFR 46.116). The term 'contract' appears to have largely (but not universally) been discontinued from contemporary usage as it arguably confuses the issues and may possibly be seen to suggest to some subjects that they must comply with certain procedures. I will return to this point.

THE ELEMENTS OF CONSENT AND CONTRACT

Arguably, there is always some degree of overlap between

consent and contract. Both require capacity (which Reed sought to address by only accepting adults as participants). Nowadays of course, the research community is more sophisticated and a contemporary notion of capacity would consider additional matters such as the would-be subject's mental development rather than just their chronological age. A clear agreement is also required for both informed consent and a contract, and a signature is often convenient evidence of this, as would anything to evidence exactly what was agreed – so a written document can be helpful to both the consent process and the fact of a contract. The question of payment may be met with when seeking volunteers and is certainly commonplace in Phase I research involving healthy volunteers. Payment, being a form of 'consideration', is often evidence of the fact of there being a contract rather than just some other form of agreement. The point in all this being that consent can be but a fine line away from a contract – as shall be seen.

Consent means agreement, and in the context of human participant research at least, implicitly and in practice, this means that the consent is an on-going process. It is in recognition of this fact that the participant is always free to withdraw, and may do so freely, at any time, without having to justify their actions. A contract by contrast is far more rigid and binds both parties upon agreement, and tends to do so even where a party did not properly understand the contract.

A consent form is not consent. The form may only be evidence of consent being discussed and perhaps obtained, and the matter is therefore open to refutation. A signed consent form will not actually prove that the signatory understood what was signed. A contract signed and dated, by contrast, is itself evidence of the fact of there being a contract (L'Estrange v F Graucob Ltd.). The present author is certainly aware of documents prepared and used in recent years by the pharmaceutical sector in Phase I studies, which have been entitled on page 1 as "Information and Consent Form", which by the time the participant is asked to sign are re-headed "Informed Consent and Contract Form". This all leads to questions such as when does consent to be a research participant become contractual – and thus have obligations attached? And if a contract is created, how does it benefit or disbenefit the parties? In this paper, I shall try to answer these questions. We can start by looking at the differences between consent and a contract.

Three elements are widely held to constitute informed consent. (1) The agreement must be made voluntarily without any undue influence, coercion, pressure and so forth; (2) the consenting parties must be competent to make rational decisions (this may be presumed if the volunteer is an adult); and (3) there should be opportunity for a full and frank exchange of all relevant information, including the opportunity to deliberate upon the matter. It was all set out so nicely as the first point of the Nuremberg Code:

"1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiments.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."

For the formation of a contract, by contrast, there are normally held to be five requirements whose presence will satisfy an English court of the existence of a contractual arrangement, as opposed, for example, to a mere promise to do something for no return, and for which failure to perform is not actionable.

There must be (1) an agreement between the parties (and 'offer' and an 'acceptance'); (2) an intent to be bound by that agreement (an 'intent to create legal relations'); (3) certainty as to the terms of the agreement; (4) capacity to contract; and (5) consideration.

Most of these points are relatively straightforward, but I shall deal with them all in due course. For the moment however, as for 'certainty', it is not so much that the parties necessarily understand the terms, but rather that these terms and clauses are capable of being given a clear meaning that

is key. Generally, English law finds a rebuttable presumption that where the parties are in business that the agreement is meant to be legally binding. Use of the phrase 'contract' by the pharmaceutical concern would thus tend to support the intent. We will however see that the term does little to benefit the subject (because of the magical clause – 'free to withdraw at any time, without incurring any penalty - which already frees the subject from most of their obligations under the contract) but it does appear to offer the researcher some possible benefit of a psychological nature, which may be exploited by the pharmaceutical company.

CONSIDERATION

Consideration turns what might otherwise be a mere 'gratuitous promise' into a contractual agreement. Consideration is usually described as some benefit to the person making the promise or some detriment to the person to whom the promise is made, or both. If this is still confusing, for the purposes of our analysis we can think of money as the benefit, so where a subject promises to participate in the study in order to get money there is clearly consideration. Consideration is often in the exchange of money, but consideration can exist without money, so long as at least one of the parties can be seen to get an economic benefit.

Nor need the amount of consideration be 'adequate' either (after all, who is to say what would be adequate in any particular situation?). The law merely recognises that its very existence be deemed 'sufficient'. This position seems to mirror the situation whereby ethics committees do not need to look at whether the money on offer is 'enough' but rather need to concern themselves only with whether it might be too much, and of such an amount as to tempt someone in to the research against their better interests.

GRATUITOUS PROMISE

When one merely promises to do something for no return or for no 'consideration' - which admittedly is not very likely in Phase I research but may be in a later phase or other medical study - and then reneges on one's promise, there is usually no legal remedy available to the other party. Suppose one agrees to be part of a research trial going on over a lengthy period of time, perhaps a year or even longer, one takes a blinded tablet (trial medication or a placebo) and gives blood samples occasionally, thereby allowing the researcher to collect data to inform the research. However, despite being in the study for some considerable period, the subject may decide that enough is enough and withdraws. The data the researcher has collected may suddenly prove useless because the object of the study was to find out how the drug performed over a lengthy period and/or in connection with a certain genomic subset. The experiment is ruined by this additional non-completer. As Ganter notes: "Retaining … subjects throughout the study can make the difference between losing out to a competitor and launching a profitable new product". What remedy has the researcher? None. Any agreement for which there is only gratuitous agreement means that there is no contract, and nothing to legally enforce. The incorporation of the clause advising the research participant that he or she can withdraw participation at any stage without negative recourse thus has no additional legal safeguards for the participant in situations where there is no consideration. Thus if they withdrew in a situation where there was no consideration even where there was not the obligatory clause, there would still be no legal sanction that the researcher could instigate against them. The clause may thus here appear to be generous of the researcher, but in truth, it is just recognition of the reality of the situation. Where there is no consideration there is no legal obligation because there is no contract. Of course, there may be a moral obligation felt, but that will be for each of the parties and a question for their consciences.

PSYCHOLOGY

Again we are back to wondering why some pharmaceutical companies might still want to use the phrase 'contract' when at best, because of the 'get out' clause, the 'contract' is in effect a unilateral contract (where only one party – here, Pharma - is obliged to fulfil its obligations) which does not bind the participant. Perhaps the pharmaceutical company might wish to use the term to reassure the participant that there is a legal agreement that offers the participant certain protections, especially should things not go as hoped. That certainly is a possibility, and it is just possible that a pharmaceutical company might favour use of the term if it might subtly intimidate some subjects into doing what they are told, as Capron (supra) could imply.[8] The term, in this light, may thus have a psychologically exculpatory effect. It is certainly suspected, at least anecdotally, that many healthy volunteer clinical trial participants do not really understand what they are letting themselves in for. Their motivation is often portrayed as blind money. They may thus not necessarily understand the true, nugatory, nature of the contract's hold over them. More research is perhaps needed here to understand whether such participants do indeed think they have signed a 'contract', and if so what this means for them.

LACK OF UNDERSTANDING

The law tends to regard the written contract as defining what has been agreed between the parties. This is so even where one party subsequently can demonstrate that they did not properly understand what they were signing or even if they did not bother to read it (L'Estrange). This fact may be helpful to the researcher qua offeror, who can then rely on the fact that the contract allows for (albeit perhaps unspecified) reductions in pay where the subject has arrived late on certain days. Contract law does not require that there be reciprocity however, and this can be witnessed by the lack of contractual arrangements for those situations where the subject is 'asked' to come in on a different day or time due to the practical exigencies of the trial.

A contract must also be unconditional (Tinn v Hoffman). If a subject wishes to discuss a protocol and subsequently only engage with it on their own terms, then one might expect any consent document (or contract) to be re-written to reflect the true agreement of the parties. However, if they do this, this might imply that the researchers could also amend the document – and perhaps rephrase that bit about 'free to withdraw'. Surely, the principle of discussing the consent document is exactly what an ethical perspective would wish to encourage – but the practicalities of doing so (the ethics committee would expect the opportunity to approve the amended document) becomes just too difficult. However, where the subject (an individual) is asked to sign a standard terms contract with a business or professional, that contract is a 'consumer contract' and thus the provisions of the Unfair Terms in Consumer Contracts Regulations (1999) apply, and any terms which are not plain, are liable to be unenforceable, at least against the individual.

THE CONTRACT'S TEETH

If the five ingredients of a contract are present then there is a contract ipso facto. The term 'contract' need not be used. It is the presence of consideration and a finding that there was an intention to create legal relations that gives rights in contract law to the consenting subject who wishes to sue. The desire to sue might arise for instance where payment is not as expected, and this may occur under a range of scenarios such as I now illustrate. Despite the fact that the contract gives rights to the subjects, this writer is not aware of any UK cases where such rights have been claimed through the courts. Such matters would generally be settled out of court.

A contract is in general a binding thing. Sometimes however exterior circumstances may change and one of the parties may want to modify the contract in order perhaps not to suffer from the new situation. Let us suppose that it has been decided that all research on new medical entities should include a certain test at some stage in the drug development process. The researcher may feel that the earlier in the drug development stage the test is done the better, and may now wish to do this extra investigation on those subjects who are already engaged in the research. However this will require those who thought they had almost finished with the trial and are looking forward to going home, being required to stay on for extra procedures. Any such modification to a contract is however generally not legally binding unless supported by new (and agreed) consideration. The subjects could thus say 'no' to the new proposals and expect to complete the trial as originally set out to them, and take the full sum owed to them as agreed. The researcher certainly cannot say no more money is due to them for the extra test because, for example, they were already present in the unit anyway. Any change in the terms of a contract is not enforceable without agreement and new consideration.

The general rule in contract law is that performance must exactly match the requirements stipulated in the contract – 'entire performance' is the expectation. If one party fails to fulfil the whole of the contract, then the other party need not pay anything at all. In Cutter v Powell a sailor died and his subsequent inability to complete the contracted voyage home meant that his estate was not entitled to any part of the sum contracted for as wages. Where it is only a warranty, or (if in a non-serious way) an innominate term, of the contract that is breached, the doctrine of substantial performance established in Boone v Eyre may however be invoked. This may allow a party who has performed with only minor defects to claim for the price of their work on the contract less any money the other party will have to spend to remedy the defect. In a situation of Phase I research it is unlikely that failure to complete a trial will be regarded as other than a fundamental breach of contract, and so no money may be due - were it not again for the obligatory clause in the contract that permits such withdrawal.

It is the case that a 'contract' may be said to be severable where payment becomes due at stages of performance, rather than in one lump sum at completion. In such cases, while a contract may not originally have been intended to be severable, one party may agree to accept and pay for part-performance. Where circumstances suggest this has been agreed, the claimant would sue on a quantum meruit to

recover the cost of such performance as has been provided. If our volunteer withdraws though, the promisor will have no choice about the matter, and so the courts would not infer such an agreement, but this is immaterial to the volunteer as the withdrawal clause overcomes this obstacle.

The subject who wishes to withdraw halfway through the trial may have an expectation of half pay. However the researcher may feel that although the subject has indeed stayed in the trial for half the time the trial is expected to last, because the second half of the trial is to be more involved it may be the researcher's view that the prorated sum due should be distinctly less than half.

In fact, as ICH-GCP (E6) points out, this matter should have been agreed before the trial commenced, as it is a responsibility of the ethics committee to confirm:

"3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written consent form and other written information to be provided to subjects. The way payment will be prorated should be specified." (Emphasis added).

However, in the UK it probably will not have been because The Medicines for Human Use (Clinical Trials) Regulations 2004 defines 'good clinical practice' as only those matters which are specified in Schedule 1 of the regulations. Furthermore, Schedule 3, which details those matters to be addressed in the application document that must be provided to an ethics committee in order to help them to form an opinion, only seeks a description of "the arrangements for remuneration of, or reimbursement of expenses incurred by, subjects" and so does not go as far into the detail as ICH-GCP. However, a claimant will surely bring the ICH-GCP requirement to the attention of the court as being a legitimate expectation and the court may well consider that such details should indeed be properly described before the trial, rather than derived in some way after the fact.

Penalty clauses (intended to pressure the subject into performing rather than off-setting legitimate losses caused by the subject's failure to adhere to an agreement) are invalid (Dunlop Pneumatic Tyre v New Garage).

If a supervening event makes the continuation of the trial pointless, the contact will be frustrated and no money need be paid unless one party has already received a valuable benefit in which case it would have to be paid for.

As noted earlier, the healthy volunteer trial arrangements are likely to be regarded as effectively a unilateral contract. In such contracts part performance cannot be revoked (Errington v Errington and Woods ; Daulia Ltd. v Four Millbank Nominees Ltd.), thus once the trial has started the pharmaceutical company cannot merely stop the trial and send everyone home – at least not without having to pay them.

Where one party is prevented from completing the contract by some fault of the other they can claim either quantum meruit (such as the prorated sum envisaged by ICH-GCP – para. 3.1.9) or, and more likely in our scenario, for full payment under breach of contract.

Of course, not all research is governed by ICH-GCP and so the question of severability or breach of contract may actually arise. For example, in qualitative research the impecunious student researcher may have rashly offered to pay £25 towards participants' travel and other costs to help them get to the interview. The question that may arise is should this sum still be paid to the interviewee who turns up (late), and then barely five minutes into the interview exercises the option to withdraw (without offering to justify themselves).

It is not clear if the offeree has or has not undertaken to complete performance. The agreement containing a clause to say that the offeree may withdraw at any stage certainly seems to leave the option up to them. In such circumstances, should the offeror have a reciprocal right to revoke the offer at any time? There are two main opinions about this. Some argue that once there has been substantial performance the offer cannot be withdrawn. Other academics see the offeror as making two offers – the express or main offer that payment will be made upon completion, and an implicit offer which accompanies the main offer that the main offer will not be revoked once performance has begun. Neither view though quite addresses the situation of the interviewee who withdraws after barely beginning and yet still seeks full reimbursement. But in reality it is unlikely that in this situation there would be found to be an intention to create legal relations – it is student research after all, and not any form of commercial enterprise.

PROMISSORY ESTOPPEL

When a contractual relationship exists then there is the possibility that one party could invoke the equitable remedy of promissory estoppel. This would arise where there occurs an obvious and unambiguous promise by one party not to

enforce his full legal rights under the contract. The promise may be implied by conduct, but silence or a failure to act will not normally be sufficient. The party, which was promised something, must have acted in reliance on the promise. The doctrine can only be invoked where it would be inequitable for the promisor to go back on his promise and insist on his strict legal rights. Thus if the researcher's conduct indicated that it did not matter that the participant had returned to the unit much later than stipulated and if he went on to take various blood and other samples and tests, then the researcher could not later argue that the late attendance amounted to a breach of contract and thus that no payment was due. Here, again, the law benefits the subject, and again of course, the withdrawal clause would effectively prevent the researcher from using the promissory estoppel remedy against any action, or 'promise', made by the subject.

BENEFIT TO PHARMA?

Arguably, the main benefit of using the term 'contract' in a consent document would be if there was a psychological one of taking advantage of subjects who may know little of the law and believe that the 'contract' places them under some legal obligation – notwithstanding the presence of the loophole in their favour. Indeed the 'free to withdraw' option can only have been introduced to negate the otherwise contractual hold over the subject. The actual use of the word 'contract' has no real legal relevance, as it is the presence of the necessary ingredients that will determine whether a contract exists, and not the mere use of the term.

A contract allows the remedy of misrepresentation, and here this would seem the only feature of a contract that just might be useful to the pharmaceutical company – if, that is, there proves to be no credence to the speculated psychological effect the term ('contract') might have with some recruits.

Misrepresentation occurs where one party makes (1) an untrue statement (2) of fact, which (3) induces the other to enter into the contract. If the researcher allowed a volunteer to enter a trial because of that subject's false statement that there were no contrary medical reasons for excluding them (e.g. that they had never taken any illicit drugs), then not only could the volunteer's own health be put into danger, but the reputation of the research unit might become tarnished and there may well be a waste of resources. Such misrepresentation will allow the offended party to make the contract voidable, and perhaps seek damages.

Until recently many seemed to regard the consent process involved in medical research as obviating a contractual situation. This may have been more an example of wishful thinking however, as I have hopefully demonstrated that the contract exists simply because of the presence of certain elements that may come together and which go beyond those required for mere informed consent. In the United States, for example, Grimes v Kennedy Krieger Institute [KKI], the Maryland Appeals Court did indeed dismiss such a false notion. In that case, because the participants were offered between $5 and $15 plus occasional "gifts, trinkets, [and] coupons for food, etc." this was evidence of there being 'valuable consideration'. It was thus held that the fact that KKI required the participants to sign a consent form only indicated that the appellants were agreeing with KKI to participate in the research study with certain expectations. That they would be compensated if things went wrong; that they would be informed of all the information necessary to enable them to freely choose whether to participate, and to receive promptly any information that might bear on their willingness to continue to participate in the study. The fact that the parties could freely withdraw was merely a means by which the contract could come to a close after which no further consideration would become due.

CONCLUSION

Consent can become contractual where consideration is given. This is only good news for the healthy subject-participants though as it gives them the protection of contract law in circumstances where they are not even tied into fulfilling a contract. It allows them, as we sometimes say in England in such situations, to 'both have their cake and eat it too.'

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