A plutocratic proposal

By Alexander Masters

If mega-rich people could buy places on clinical trials, would this help drive forward the development of new treatments that could benefit everyone? Alexander Masters thinks it might just work.

This article appeared in the Wellcome Trust's (now discontinued) emagazine, Mosaic, on 27/10/2014.

"But you have missed the bigger idea!" exclaimed Peter Lanciano, grabbing the pepper grinder and banging it on the table. "The problem isn't how to get my drug into Mr Pepperpot. The problem is how to protect me from being sued if Mr Pepperpot dies."

It had taken me two years to track Lanciano down. For this meeting I'd broken off my holiday, woken up at three in the morning and flown 1,000 miles across Europe to have breakfast at a London hotel built like a penitentiary. Lanciano is the Executive Director of a small US drug company. In his early 50s, with a Teddy Roosevelt moustache and a lumberjack shirt stretched tight across his broad chest, I believe he can help solve a niggling problem that holds back medical research around the world and makes patients suffer. Every year, an untold number of potential new drugs or interventions, any one of which might go on to improve thousands of lives, are thrown away without being tested in humans. It is a matter of funding, not science: there is not enough money in the public or private sector to run clinical trials on every exciting proposal that comes out of research labs. Thoughtful but hurried (and often arbitrary) judgements are therefore made about which products to save – and the rest of these potentially life-saving therapies are ditched. "**There's tons of promising stuff out there," says David Stojdl, cofounder of the Californian biotech company Jennerex Biotherapeutics, "and it is dying on the vine."**

I have a simple proposal for a way to rescue this waste. I'm not a scientist or a physician; I have no medical training. I'm a biographer and an illustrator, and until a couple of years ago I'd never heard of clinical trials. But I know my idea works because I've already tried it once, to rescue a promising anticancer therapeutic that was about to be thrown out in Sweden. The general version of my proposal has now received backing from a select group of university research departments and a clutch of experts on medical ethics, and has the interest of one of the world's largest law firms specialising in the life sciences. If the scheme can be made to work on a larger scale, it will open up the possibility of millions (I think, billions) of pounds of extra money for clinical trials, especially for rare and difficult-to-treat diseases – the ones that traditional funders are reluctant to support.

First, the background: in 2007 my best friend in the world, Dido Davies, was diagnosed with neuroendocrine cancer of the pancreas – the same disease that killed Steve Jobs.

The main ways of treating this uncommon cancer are the same as they were half a century ago: surgery, radiotherapy and chemotherapy. Surgery cures solid-tumour cancers, if you catch them early; but be a day late and there's a good chance that the ghostly disease will pause, become no more than a murmur in blood tests for a year or two (or ten), and then re-emerge with ferocity in the liver, or brain, or bones. Surgery and radiotherapy can be used to try and stop cancer that has spread, but it's often futile. Dido started with chemotherapy. Invented over 60 years ago, it is usually clumsy, frequently has horrific side-effects and is sometimes fatal. Once I came into her hospital room to find her bed empty and the tubes on the drip-feed stand dangling, wrenched out of her arm. Dido was in the toilet. The violence of her vomiting was like the sound of three men arguing.

I started to look for something better. My idea was to find the labs devising new treatments for this disease, then to sweeten up the professors so they'd accept Dido onto their clinical trials as soon as possible, before disease or the standard therapies killed her. I wanted nothing that was quack medicine. For Dido, I wanted a new treatment from a world-class lab, which had published in world-class journals, was directed by world-class scientists, and wouldn't torture her wonderfulness away or destroy her brilliant brain with chemicals.

I found one. A team at Uppsala University in Sweden (the university's hospital is a European Center of Excellence for the treatment of neuroendocrine cancer) had published preclinical data, in international, peer-reviewed journals, of a startling new drug that caused tumours in mice to melt away. That doesn't mean much in itself – kitchen bleach has the same effect – but along with the rest of the evidence, the researchers had proved the idea had promise. Ad5[CgA-E1A-miR122]PTD, to give the compound its full tooth-breaking name, was a remarkable therapeutic. It was not just that the Chairman of the European Neuroendocrine Tumor Society had wanted it to be tested in humans by tomorrow morning; it was the fact that the drug was a bug. Known as an 'oncolytic virus' – a virus that specifically targets cancer cells and leaves ordinary tissue alone – it would be cheap to produce, simple to administer and have few suspected potential side-effects beyond mild flu. If the promise of the Uppsala discovery were even partially borne out in human trials, it would ease the suffering of many lives.

But it had been shelved.

No one would provide the £2 million needed to start the clinical trials.

For drug developers, there's not much interest in rare cancers; for scientists, after the initial lab excitement of discovery has worn off, there's little opportunity for glory left. Pushing new ideas into clinical testing is tedious, exhausting and takes time away from making other discoveries. Promising work that offers alternatives to the savage old therapies for such diseases is therefore difficult to fund and quickly forgotten. There were no suitable EU grants for the Uppsala work; Swedish cancer charities have shallow pockets, and the Swedish government refuses to support clinical trials as a matter of policy. Even if a private company could be involved, the patent situation was muddy, the target population small and the commercial risks unusually high.

It was then that I had my unexpected funding idea. As far as I knew, no one had ever tried it before. I flew to Uppsala to meet the lead researcher, Professor Magnus Essand, and asked him, if I could raise the cash he needed, whether he would restart work on his unpronounceable bug.

Eight months later, the £2 million was on his table.

To non-doctors such as myself, it appears too glorious to be true: a virus that specifically targets cancer cells. After months of coming out of oncology wards sickened by the well-intentioned torture and clumsiness going on inside, it seemed to me like the stuff of dreams.

Today, supercomputers flick steadily through millions of molecular arrangements, searching for new chemicals that will interfere with one or more of the mutations that characterise a cancer cell; vast machines prickling with syringes perform test-tube experiments 24 hours a day, 365 days a year. The organised, worldwide hunt for new drugs to combat metastasised cancer clatters on in shiny research buildings from Beijing to Bombay. The difficulty is that cancer, especially neuroendocrine cancer, is not a single disease, but a crazed hotchpotch of disorders. Each tumour can contain dozens, if not hundreds, of genetic mutations, some of which could allow fatal growth; attacking them one at a time is like trying to stop the tide coming in using a shovel. The trick is to find medications that interfere with all of these mutations all at once.

That's the appeal of viruses.

To virologists and molecular biologists the idea makes perfect sense. Healthy cells are programmed to die when they become infected by a virus. They are altruistic, because their suicide prevents the virus breeding and spreading to other parts of the body. But a cancerous cell is immortal – that is one of its defining characteristics. Through mutations, healthy cells manage to turn off the parts of their genetic programme that cause them to die: cancer is the disease of too much life. So, because cancerous cells refuse to die when infected, the virus is able to multiply inside them. Eventually, the sheer volume of the virus's progeny becomes too much and they burst through the walls of the cancerous cell, killing it. These free-floating viruses then infect further cancer cells or are eliminated by the body's immune system in the usual way. The virus becomes, in effect, a cancer of cancer.

But the reason cancer is fatal is not just because it turns modest, mortal cells into immortal, rapacious ones – it's also because it (taking advantage of yet further genetic mutations) makes these corrupted cells invisible to the most powerful protection mechanism in the world: the human immune system. The second way in which a virus can lead to remission in cancer is by making tumours visible again. By virtue of the virus's massive proliferation, the immune system finally spots there's something amiss. Viruses turn a previously invisible tumour into a beacon of disease.

My idea was this: there are over 100,000 people in the world worth more than £20 million. According to medical statistics, between three and five people in every 100,000 get neuroendocrine cancer every year. So, three to five supremely wealthy people will have neuroendocrine cancer.

For £1 million, I was going to sell one or two of these plutocrats a place on Professor Essand's bug trial.

When I look back, I'm astonished by how little work I had to do to raise the £2 million. I got back to England, wrote an article about the bug for the *Daily Telegraph*and waited. I didn't

have any other plan. I didn't mention that I was planning to sell trial places. I was fairly sure it wasn't ethical – though I didn't know why not. Perhaps simply because, when you're a patient or the friend of a patient, medicine so often seems to be denying you access to good things on 'ethical' grounds. But I had a gimmick. I had got Essand to agree that he would give up the unpronounceable moniker he'd given his bug and rename it after anyone who donated the first £1 million. The *Financial Times* pharmaceuticals correspondent picked up on that. The editorial page ran an amiable paragraph poking fun at the idea: new drugs are notoriously risky however good they might seem in the lab – so what would happen if this remarkable forgotten virus turned out to kill people? Would you then be allowed to name it after your worst enemy?

Two weeks after my *Telegraph* article, the newspaper surprised me by publishing a brilliantly written reply piece titled 'Would I take an untested cancer treatment myself? Hell, yes!' It was by Dominic Nutt, a communications specialist who had worked for humanitarian and aid agencies. He'd been kidnapped, shot at and bombed, but when his doctor had told him he had a neuroendocrine tumour on his appendix and might not see his daughter's first day at school, he had broken down in tears. A few days after his article came out, he and I met on the balcony of a Wetherspoon's pub in Victoria train station in London. He introduced a social media advisor, Liz Scarff, and I included Colin Midson, who runs a literary consultancy, Bookshaped. None of us knew much about cancer. On Dido's birthday, **we launched iCancer** through a crowdfunding page on Indiegogo.

The *Telegraph* articles came out in August and September 2012. By the spring of 2013 the money was secure. Of the £2 million required, £200,000 had come either directly or indirectly (i.e. by inspiring donations through other routes) from the crowdfunding website. In order to support the campaign Dom and I had run an independent peer review to check Essand's research; **we'd bothered world experts in Canada and Oxford and Manchester and London. All had been happy to talk and agreed that Essand's work was interesting, not quackery, and had potential. Peer review is not a mysterious or difficult process. But the crowd added something extra and even better to this traditional approach – mass suspicion.** Every interested person wanted to double-check the scientific value of the work, the honesty of the fundraising, the percentage lost in overheads, the reputation of the university. They spoke to their physicians, looked up the rankings of journals, devised cheaper ways to get donations directly to Uppsala, and when there was a hitch in the transfer of some money from America, they quickly found the best of their number to sort it out – and lo, it was sorted out. The work of the crowd, once it took the idea of Uppsala on, was inventive, invigorating and invaluable, but also judicious and kind.

The balance of the money came from an Arizona oilman called Vince Hamilton. He'd read the articles in the *Financial Times* over breakfast in a café in Geneva. He too had neuroendocrine cancer. The money needed was small in his terms – less than a tenth of his wealth. Just as Dom and I had hoped, he understood the unwritten offer instantly. He contacted Uppsala and offered Essand the balance in return for guaranteeing him access to the new drug as soon as it was ready. In fact, he went considerably further. Vince not only donated this vast sum of money to enable Uppsala to start a clinical trial, he immediately put his business expertise to work to find out how to lower the costs, and shortly afterwards set up a $20 million fund to promote research into further drugs to treat neuroendocrine cancer.

In June Essand took the virus back out of the freezer and started the process of setting up a trial, with Dido and Vince both promised access to the drug the second it was ready. Because of all the regulatory delays involved in starting human tests, this would be in one to two years' time.

I wrote a second piece for the *Telegraph* celebrating the success of the campaign.

Dido died on the morning that it was published.

For months after Dido's death, I couldn't bear to think about medicine again. I didn't want to have anything to do with Uppsala or Dom or Liz. I detested everything about neuroendocrine cancer. I was startled out of sleep at 3am by images of Dido's last days. By and large the NHS had behaved magnificently with Dido, but after the first dose of chemotherapy temporarily shrank her tumours, nothing worked again: as if insulted by the assault, they grew to a gargantuan size; they became inflexibly deathly. Perhaps it had been a bad idea to give her these poisons as her first line of therapy. But misjudgements are part of the disease. Cancer does not proceed predictably; there is as yet no way to determine in advance what treatment will be effective for neuroendocrine tumours and what will not only weaken the patient further with side-effects but also urge the growths on, making them the size of grapefruits, then footballs. As one consultant said: "In fifty years time we will look back on this period in cancer treatment as an Age of Barbarity."

In February this year Vince's condition suddenly worsened, and he died in March. His widow immediately confirmed the donation to Uppsala and took charge of his $20 million philanthropic fund.

I began thinking again about the fundraising we'd done. **Why not extend the principle of selling trial places, to raise money for other Uppsalas and other diseases: not just neuroendocrine cancer, or just cancer, but any illness?** There are over 12 million millionaires in the world – any one of these would want to buy a place on a trial if it might purchase relief or stave off death. **Every one of them has people they love for whom they'd pay good money to get an extra chance. Why not set up a charitable or private body that would arrange these 'sales'?**

My first thought was that it would be run like a dating agency.

Let's say you take select number of peer-reviewed research projects that have produced a compound or intervention that could treat a certain disease, but that have stopped research because of a lack of funds. Crucially, they have not stopped because the science has been shown to be no good. Such projects will typically deal with rare diseases (and **54 per cent of cancer deaths are from less common cancers)** or with diseases that progress so slowly that it can take up to a decade to reach their end point (such as the death of the patient), making the trials expensive. Other reasons why such research might not be able to secure traditional funding is that the science is novel, and **the large, established funders are generally conservative and want to stick with what they know, or the research team has been worn out by bureaucratic fighting, and wants to do a different project that's easier to promote.** All these difficulties applied to some degree in the Uppsala case.

The 'Dating Agency', after ensuring that each piece of research is scientifically sound and from a reputable institution, then puts the selected projects into a 'market', which is open to the crowd:

people offer specified sums to get a given project up and running, in return for specified benefits –

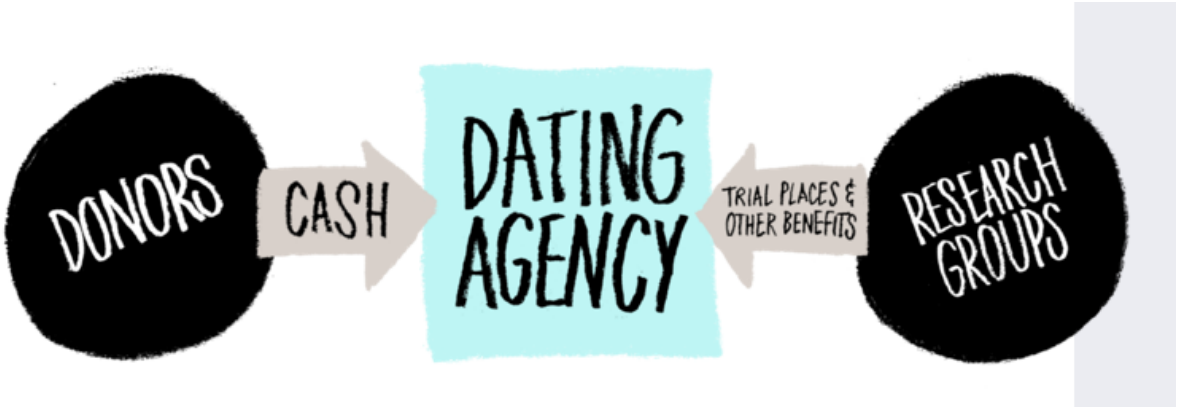
the most expensive of which is a place on the clinical trial.

Other benefits might include (if possible): naming the new drug or procedure, as at Uppsala;

naming the entire project;

a mention on all subsequent research papers as a principal funder; a tour of the lab;

a week's crash course in cancer medicine at the university involved; and so on.



Model 1. In this, the simplest model of the idea,

trial places (and other benefits) are advertised and 'sold' through an organisation that does little more than act as a Dating Agency or matcher, and which is run through a website.

The website provides information, listed by disease, about promising projects that are close to trial stage and willing to sell places, and relevant contact email addresses.

The 'little more' this agency could also provide would be such things as:

a scientific monitoring committee to ensure that quack medicine does not use the site;

??? information about how donors can set up an independent peer-review process;

a forum in which donors and companies can discuss how to improve the process and highlight complications as they occur;

a help page, with useful links, for turning the fundraising into a more general crowdsourcing campaign; and

a contact list for medical lawyers, medical publicists, contract research organisations (if the parties decide to outsource the trial), etc.

I broke the proposal into three aspects: its ethics, its legality and its worth – both medical and commercial. I needed to put the Dating Agency proposal through a series of trials to prove its safety, efficacy and worth. It would be similar to the process of introducing a new drug, I told myself. If the idea passed, or failed in a spectacular or comical way, I would write this article. I figured that my chances of success were about the same as a new drug's too – i.e. 1 per cent.

I began with ethics, because I didn't know what the word meant. Is it the same as morals? Why do research trials need to be approved by ethics committees, but not morality ones? It is clearly inhuman to deny dying people access to trial drugs that might help them, yet that's exactly what happened with HIV patients in the 1980s. Those dying men had to raise a howl of protest to overcome this 'ethical' decision. Ethics committees are composed of kind, thoughtful, experienced people from all walks of life, but it's clear that their decisions can be immoral. Lawyers have a glib saying to help separate the two ideas: "Morally, I might find it repugnant to defend someone I am certain is a rapist; ethically, I am obliged to argue his case as though convinced he is innocent." Ethics is an institutional code of conduct; the aim is to ensure fair treatment and benefit to as many people as possible. Morality relates to private beliefs. However, with medical ethics committees (which have the ability to stop new drug trials, among other things, and are not composed of professional ethicists) there's also a strong element of public relations. **A decision once considered ethically correct (to deprive HIV patients of promising but incompletely tested drugs) is reversed when it turns into a PR disaster, and lo! the new decision is also ethically correct. It's a complicated subject.**

Phase one – ethics: I talk to ethicists

Julian Savulescu is Professor of Practical Ethics at the University of Oxford and Editor-in-Chief of the ***Journal of Medical Ethics***, ranked by Google Scholar as the world's number one journal on bioethics. His faculty photo shows a pugnacious, handsome man in his mid-40s with outdoor shoulders and the determined face of a bush ranger (he is Australian). He must be a hard man to please, I figured; so I emailed him first.

"Sounds like a great idea," he emailed back. "What do you want me to do? We can arrange a time to Skype if you want some quotes supporting it."

His Skype photo shows an empty room. (Is that philosophical humour, I wondered, or is he practical only in ethics?) When he answered the call, he did not turn on the camera. I was much too timid to ask why.

"The biggest complaint about your scheme is going to be that it means r**ich people are getting treatment and poor people aren't. But you've dealt with that by ensuring benefits go to people who can't afford the treatment."**

This is, in fact, critical to the scheme. An early-phase clinical trial might involve 15 or 20 people; so, to set up a personal trial, the wealthy donor also has to pay for 14 to 19 poorer patients. There is no way round that. **The donor is shackled to beneficence**. Savulescu

believes this necessary generosity is vital to funding medical care in the future. "People don't understand that there's an extraordinarily limited health budget. People are denied access to interventions and treatments all the time because it's too expensive to provide them. You could find cures for these rare forms of cancer very quickly if you put enough money in, given the huge advances of science, but it's too expensive, and if you rely on conventional funding modes it is just not going to happen. I had a similar idea to yours: there's this new form of cancer therapy called proton therapy. It's very expensive and delivers very high doses in a very precise way with much less tissue damage than other treatments. My idea was, why don't you build a state-of-the-art facility and have half of the patients massively rich oil billionaires from the Middle East?"

"Half!" I interrupted. "I want only one person, to keep the sense of privilege to a minimum."

"I think you could go up to half."

"In that case, I could expand the funding base hugely. I'd only need ordinary millionaires. There are around 12 million of those in the world and they must between them have every disease going. If ten people were allowed to pay to get places, instead of one, they'd need just £200,000 each."

"It would be harder to get that many. O**ne of the main difficulties trials face is recruiting enough patients who meet the inclusion criteria and who can get to the test centres."**

"But there'd also be many more people I could ask. I could do it with the help of a crowdsourcing site."

"If you can bring in the cash through the people who can pay, but also give benefits to the other half who can't, I don't see that there are any equality concerns."

The second complaint Savulescu thinks people will make against my Dating Agency proposal is that **it's going to exploit rich people's desperation and make them throw their money away.**

I have several responses to this.

One is, "So?"

The main force that would make the Dating Agency work is clearly desperation; that's what's powerful about it. The sick, wealthy or otherwise, are desperate to find new treatments. They know that traditional therapies like chemotherapy and radiotherapy can be both savage and futile; they want something fresh, scientifically decent and ready to be injected when that day of despair arrives. **Doctors like to say we mustn't play on patient desperation, but that desperation never goes away just because doctors are pompous about it.** The Dating Agency provides a way to guide this enveloping terror towards things that might actually help, from responsible sources; it stops good money being wasted on quack ideas.

Wealthy people financing clinical trials is not new: this type of private funding already exists all over the world if all you want to do is make money. As Savulescu said, "If I were a venture capitalist, I could invest millions of dollars in funding the development of a drug, hoping to make hundreds of millions of dollars if it's successful. So why

shouldn't I be able to pay the same money for the same development, to have a chance of saving my life? It is completely ludicrous."

With this support my idea had passed my first test, but Savulescu (who these days I almost dare to think of as 'Julian') does have a certain reputation as a controversialist. So I wanted more.

"It's just all so fascinating," emailed the next ethicist I picked. "There's loads to talk about!" He invited me to meet him. Energetic, round-faced, with heavy-rimmed spectacles and darting movements, Dan O'Connor is Head of Humanities and Social Science at the Wellcome Trust, and one of only two or three ethicists in the world who specialise in the effects of crowdsourcing on medicine.

"When I began studying this field I was literally getting feedback from journal editors saying 'Facebook isn't important. It's not an area of interest. It's a passing phase,'" he said, widening his eyes, still amazed. He hurried me past the smooth Wellcome Trust security gates into a vast atrium, beaming with sunlight and polish. At the ends of this airport-style enclosure, lifts elevated steady streams of bright-faced employees up to glass-fronted floors.

The moment we sat down in the atrium café, O'Connor began darting at my Dating Agency idea, stinging it like a bee.

The traditional relationship between doctor and patient is 'vertical', with **the knowledgeable doctor in charge directing the healthcare of the usually ignorant and powerless patient.** O'Connor calls this an 'intermediary' system. "**Social media tips that sideways, so now you and the doctors are peers. The doctors are no longer in control of the information. Everything we've done on the ethics of this is about that vertical imbalance of power.** What duty and roles do we offer to one another when we're all peers? But when you put a plutocrat buying his way onto trials in this utopian world, it completely perverts the network…it's fascinating."

"But by funding a new trial," I said, "the wealthy donor is paying for ordinary patients to join him on the trial to receive potentially useful drugs, so he gives the patient population power, because he gives [the trial] wealth."

??? DISAGREE!!! O'Connor shook his head, unsatisfied. "Once you introduce an uneven monetary relationship, it's warped the vision of trials as the social spread of risk."

But the point was more theoretical than critical, so he dropped it and introduced another possible complaint: "The question you'll get asked is, '**Is the rich person dictating the research agenda?'** People won't like that, even though the rich have done that since time began. Think of Bill Gates determining the priorities of the World Health Organization."

"But **the wealthy person is not commissioning new research. He's picking up established, peer-reviewed research into his disease that has not managed to get funding from the usual sources because there's not enough money to go round, even though it is good research.** The Dating Agency simply helps things along. It says, 'Well, we have these university departments where they have various promising things and these peer-reviewed papers to back up the work, and do you want to fund any of them?'"

This, in effect, is the role I played between Vince the oilman and Uppsala.

"What happens if the donor invests in the trial, then gets put on the placebo wing?"

He or she would throw a fit, of course. But I was ready for this one. "Either they only **fund a trial that doesn't have a placebo wing, but still allows continued treatment,** such as the one at Uppsala, or the donor insists that in return for funding the thing, he gets treated not as part of the trial, but alongside it, as a compassionate usage exemption. Such exemptions happen all the time. Why not for this?"

"Another big ethical problem. **Is it right for one person to buy themselves out of randomisation, whereas everyone else is taking the risk?"**

This seemed a significant sting to the Dating Agency plan, but O'Connor appeared, if anything, to be getting keener on it and buzzed pleasantly over his tea, waiting to see if I could figure a way out.

"Then, until we can solve that limitation, the Dating Agency will not accept randomised controlled trials," I grumbled.

In medical parlance, there are typically **three phases of trials a drug has to pass before it can be sold commercially.**

Phase I tests the tolerable dose range and safety in healthy volunteers or, in the case of serious diseases such as cancer, in sick patients. **With a few exceptions, the doses used are too small to offer medical benefit.**

In phase II the research team tests efficacy, and uses the information from phase I to provide potentially therapeutic treatment at the optimal safe dose.

This second phase of trialling can be divided into two parts: IIa, which is open to all suitable patients and has no placebo wing, and IIb, in which placebos and randomisation are introduced.

Phase III tests whether the drug is better than the best already available – **this is abominably expensive, involves hundreds of people and is not worth thinking about unless you're a multibillionaire.**

O'Connor's objection therefore **restricted the Dating Agency to brokering phase I or phase IIa trials.** That's not terrible. That's almost all it was intended to do anyway: get promising preclinical research over the hurdle into early-stage clinical trials, because that comparatively small amount of money is way beyond the reach of ordinary university departments. Uppsala is a combined phase I/phase IIa trial.

~~??? WHAT IF IT WORKS??~~

O'Connor's next objection had not occurred to me at all: "What happens if the drug works?"

"Splendid. He's bought back his life and the lives of 20 others, for a measly £2 million."

“And he’s going to want to go on having access to the drug. Very few trials are for a drug that might cure you outright. Most are to treat chronic conditions, like cancer or diabetes or HIV.”

“Of course.”

GOOD POINT
“But then he’ll have to provide it for all the other patients who’d been on the trial too, otherwise they’ll die.”

In short, the wealthy individual gives £2 million, returns home triumphant from the hospital, and finds a bill for another £10 million lying on his doormat because he’s now got to fund the drug in perpetuity for every other patient who shared in the risk of the trial in order to let him have access to it. In fact, as O’Connor pointed out, it would not be a lifelong commitment because there is well-established etiquette on this matter. A lot of drug companies say, “If you’re on this trial and it works, we will pay for you to have the drug for the next two years.” Within these two years other sources of funds will have been easy to find, because everybody loves a drug that works.

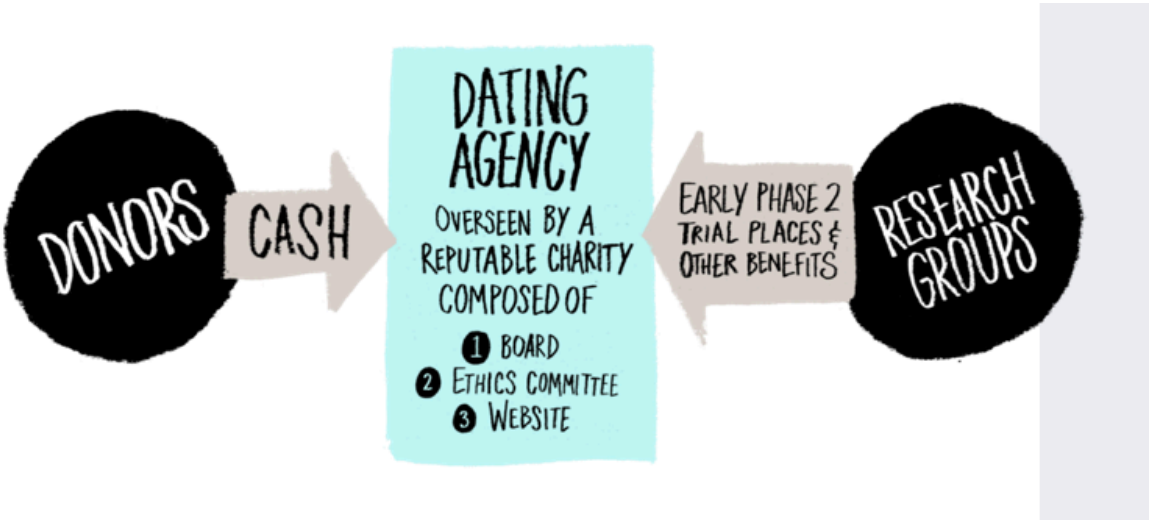
But then, added O’Connor, there’s the adjusted problem: **what happens if the drug works for some of the people on the trial, but not for the donor? He still finds a £10 million bill on his doormat, only this time he’s come home knowing he’s about to die.** “I suppose that’s just the risk of doing business in this way,” said O’Connor, answering his own question with unexpected corporate brutality – the brutality of the ethicist rather than the moralist.

Phase two – legality: I talk to entrepreneurs and lawyers

“But you guys have missed the bigger idea!” repeated Peter Lanciano, the bullish Executive Director of the US biotech company who was banging the pepperpot about at the start of this article. He, Dominic (who has teamed up with me again to promote this proposal) and I were halfway through our breakfast at the hotel built like a penitentiary.

I’d come across Lanciano’s name long before I’d heard of Uppsala. It was a set of YouTube lecture videos posted by his company that introduced me to oncolytic viruses. The company manufactures Seneca Valley virus (SVV). First isolated in pigs on North American farms by veterinary scientists in the 1990s, **SVV was accidentally discovered** to target neuroendocrine tumours when it ended up as a contaminant in the gel used to grow cancer cells. Researchers found that neuroendocrine cancer lines quickly died when dabbed on these supposedly innocuous substrates.

The YouTube videos showed the startling effectiveness of SVV against a whole range of neuroendocrine tumours – not just the type that killed Dido and Steve Jobs, but also small



Model 2. The adjusted Dating Agency model, after meeting with ethicists. The board and the ethics committees should include patient representatives, not just ethicists and doctors. The agency ensures the quality of the research being sold, and promotes confidence in both patients and research groups. The trials are not limited to being early phase II trials, but are unlikely to be anything else: phase I trials do not in general allow extended treatment; phase IIb trials introduce the complication of a randomised wing that uses either placebos or already-existing treatments; phase III trials are prohibitively expensive.

??? ANY UPDATE??? > O'Connor's observation that the donor should not, ethically, be allowed access to compassionate usage (should he or she fail to meet the trial inclusion criteria) is still to be sorted out. Uppsala is a phase I trial followed by an early phase II trial.

cell lung cancer and the childhood cancer neuroblastoma. In both of these the company had started clinical trials – but the videos had been maddening. It was only by creeping through one of them frame by frame, waiting until a few lines of small, fuzzy text on a PowerPoint slide that had been half-hidden behind a podium appeared at last in full camera view, that I could use a magnifying glass to discover the name of the company. When I checked their website, it hadn't been updated in four years. I left messages on the corporate answerphone, sent emails, tried a fax: nothing roused them. I contacted the hospitals running the trials – despite encouraging results, the trials had both stalled because of lack of funds. I managed to track down the email of the company founder, who had left the company years ago, and claimed I was writing a piece for the *New Yorker*. That's what finally got me a response.

Lanciano has provided an idea for the Dating Agency that could turn my simple proposal into a subtle one with a much broader reach, especially among biotech companies. **"What you need to do," he said, positioning, with two bangs, the table's pepperpot to the right of his plate and saltcellar to the left, "is create a fund…*here*!" – and he pointed at his plate. The pepperpot stood for the sick donor. The saltcellar was the biotech company with a promising new drug.**

"But we have done that," I protested. "That's the Dating Agency: the organising body that oversees the transaction, supplies a team of ethicists, guidance for independent peer review, lawyers to ensure the contract between the donor and the researcher is honoured."

Lanciano shook his head. “It won’t work.”

“It worked for Uppsala,” I pointed out.

“Universities are different,” said Lanciano, biting a mushroom off his fork. “Biotech companies are more closely monitored by the regulatory authorities, and under your scheme as it stands I couldn’t afford to take the risk of supplying this plutocrat with my drug.”

“But I’ve just paid you £2 million for it,” I complained, forgetting in my outrage that I was not Pepperpot the plutocrat. “I’ve enabled 20 people who wouldn’t have seen the drug at all to go on an approved trial, all I want is to join in or, if I don’t meet the inclusion criteria, be treated on a compassionate basis.”

“What happens if you die?”

“That’s a risk with all new potential therapies.”

“I’ll tell you what happens: I lose my job and might go to jail. If I treat you with an unlicensed drug on a compassionate basis outside the regulatory authority-approved trial, I’m liable.”

“I sign a legal document accepting all the risk and promising not to complain from beyond the grave if you kill me.”

“I still go to jail. The company has to close down. Everybody loses their jobs. **I’ve knowingly allowed the use of an experimental drug in a situation that the FDA [or the MHRA in Britain] hasn’t approved, and now I’m responsible for killing you. The FDA quite correctly doesn’t like it.”**

The donor’s death would not only close down the company, it would also destroy the slim chance the drug has of reaching the market and saving the people it might be licensed to treat. Looked at in this light, requests to biotech companies to provide unlicensed drugs for compassionate usage are extremely selfish.

“But if my consultant has confirmed that he thinks the drug might help, in my case? He knows the literature. He knows the drug. He’s an expert.”

“Is he? **You’d be surprised how much oncologists don’t know about their patients. On our trial for small cell lung cancer oncologists sent us patients who they thought had the disease, but when we double-checked with confirmation studies, some of these people didn’t have it. They couldn’t even get that right.”**

“What if I paid you £10 million? That’s not just to manufacture the new drug, it’s to cover the risk you’re taking if you have to treat me off-trial.”

Lanciano shook his head.

“Twenty million?”

"Not worth it. And people have crazy ideas about what they're going to do. I had Nancy Pelosi, the Speaker of the House of Representatives, ring me up to lobby me. She was trying to get someone our drug on a compassionate basis, but this person wanted to give his four-year-old daughter 100,000 times the equivalent adult dose. I was thinking, 'Oh my God, what if she has anaphylaxis and dies instantly? This company would be dead.' My issue was, 'Aspirin is a good drug, but if you give someone 100,000 times the recommended amount, she's going to die!' The *Wall Street Journal* ran an article about it."

"Thirty million?" I suggested, meekly.

This problem of liability if you provide unlicensed drugs for compassionate usage is not limited to the USA, although it is more pressing there because everybody is always waiting to sue somebody. The British regulatory authority, the MHRA, also frets about the use of unlicensed therapeutics, even for the dying. **No country can afford to let biotech companies hand out potentially lethal poisons, however do-goody the reason.**

Lanciano's solution to the problem is best illustrated by an example.

Let's say a wealthy individual is diagnosed with a mid-gut neuroendocrine tumour. He gives £2 million to the Dating Agency, which then hands it across to a biotech company that has a promising new but underfunded drug for this type of cancer. The £2 million is used to produce 100 doses of the potential medication. **As soon as the drug is manufactured to the correct standard for human testing, the biotech company gives ten of the doses back to the Dating Agency and uses the remainder to run its trials, conduct further tests, etc. One of these ten donated doses is guaranteed to be given to the donor, which leaves nine doses for the Dating Agency to distribute to poorer patients.** In total, therefore, the donor is now paying for all the people on the trial to have the drug, plus a further nine people who can't join the trial for whatever reason but are suitable for a compassionate usage exemption.

?? ABOVE SEEMS JUST AS LIABLE AS WHAT HE SAID ABOVE/ABOVE

The next part is the critical one, and is composed of several elements:

1. The donor's consultant now sets up what in the USA is called a **'Physician IND' (a 'physician-initated investigational new drug' t**o give it its full name). In effect, this gives the consultant regulatory approval to run a bespoke trial for the donor using the company's drug. The advantage of this, from the company's point of view, is that **it removes their liability** if the wealthy individual dies. In the phraseology of medical litigation, a Physician IND "transfers ownership of the data" from the company to the physician. It takes about three to six weeks to arrange.

2. The nine other, **poorer patients who can now be treated must also get their consultant's approval to use the new drug. In each case, their consultant must set up a bespoke IND.** There is no legal requirement for these extra doses – it is entirely a matter of PR. As a *Guardian* journalist I spoke to recently said, "If you didn't have them, I could write the editorial against your modified proposal this instant. One rich person getting a medical exemption for a new drug, but no one else can afford it? It looks rotten. These extra nine doses keep the thing looking honourable."

3. All of the people being treated with the new drug under this scheme agree to supply their data (i.e. the details of their illness, what happens to them while taking the drug, etc.) to the Dating Agency.

It took me two cups of coffee and a £12 croissant to get Lanciano's scheme straight. "So, the donor hands over his money in return for a promise that he will get his dose of the drug as soon as it's made…"

"Exactly. Which means he can fund any new trial into any drug that his physician agrees might be suitable for his condition. If he has mid-gut carcinoid, the trial he funds could be into small cell lung cancer – it doesn't even have to be a trial for his specific disease. But since small cell lung cancer and mid-gut carcinoids are both neuroendocrine tumours, and the preclinical and clinical studies that we've already done show that our compound might help in both cases, the wealthy individual's physician can reasonably apply for the right to use our virus."

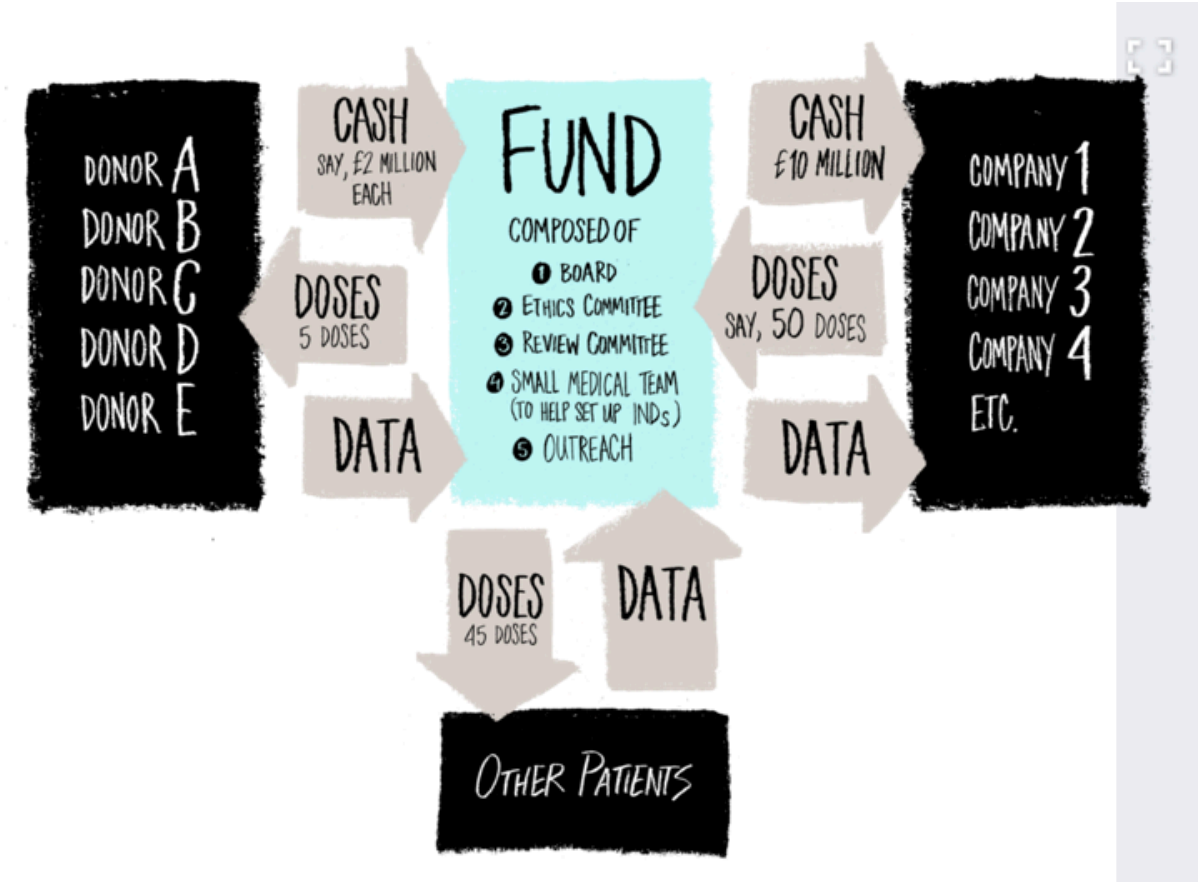
I took another bite of the gold-plated croissant, and lapsed again into the role of the wealthy individual. "**So, instead of me paying you to set up a trial that I can join, I'm paying you to set up the trial, and then to provide me with the material so I can set up, in effect, my own separate trial, just for me. What's more, the main trial, which I'm funding you to run, doesn't even have to be specifically for research into my disease – it just has to be for a medication that my consultant believes could also benefit my disease."**

"This is an industry-wide problem. Of course, **the scheme shouldn't be limited to one donor or one supplier. Let's say five wealthy people with mid-gut neuroendocrine cancer put their money into the Dating Agency, and in return they each get access to trial drugs. The money in the Dating Agency is then handed out to, say, four or five different companies all wanting to run trials into different new treatments for this disease. You want to promote as much new research as possible.** Pounds go to the companies and doses come the other way, to the patients. Let's say the companies agree to hand over 5 per cent of the doses, so if they make 1,000 doses the Dating Agency gets 50 – **they'll be for a range of different potential new treatments. The most appropriate one can now be selected for each patient. Five donors only need to consume five doses, so you have 45 doses left over for other people."**

Meanwhile, these drug companies will be getting the usual calls from all over the world asking for access to drugs for compassionate usage, just as Lanciano's company had Nancy Pelosi and the father of the four-year-old on the phone. But now the companies can reply, "Oh yes, perhaps something can be done. Contact the Dating Agency, because they have 45 doses to distribute. If your case is suitable, they will give you one and all you have to do is set up a Physician IND with your doctor." That doctor will then assume legal responsibility and ensure that a sick child isn't given 100,000 times the recommended adult dose.

Lanciano admitted, however, that one can never rule out the possibility of a lawsuit being filed against the doctor and the doctor's institution, but insisted his proposal will make such litigation unlikely. Everyone will have signed waivers; **the protocol will have been developed and reviewed by a set of respected specialists, including ethicists and the regulatory authority; and the patient, who'll be about to die anyway, will have directed the physician to take the risk.**

The advantage of the Dating Agency gathering up several donors to finance a variety of companies, producing a variety of drugs, is not simply that it encourages more research and makes more potential medications available to all the donors. It's frequently the case that **while one treatment will help one person, it will, for some unknown reason, be no good for somebody else who apparently has exactly the same complaint.** That was the case with Dido. Nothing worked after chemotherapy put the tumours into a brief retreat, even though the other interventions were specifically designed to combat her illness.



Model 3. In this example case, five donors with various types of neuroendocrine cancer give £2 million each to the Dating Agency. The Dating Agency then passes on £10 million in grants to a variety of companies that have drugs for neuroendocrine cancer close to trial stage. In return the Dating Agency receives a certain percentage of the various drugs manufactured, say a total of 50 doses. Five doses are then handed back to the donors to be taken as part of their Physician INDs (or whatever the equivalent is in their countries). This leaves 45 doses to be distributed to 45 other patients, for their Physician INDs. In other words, five donors are offering potential benefits to all the participants on five trials (around 100 people) plus a further 45 patients on special exemptions: a total of around 145 people who would otherwise not have a chance in the world of accessing these potential medications.

Lanciano is a corporate man, and a drug entrepreneur and plutocrat himself. He is involved in several venture capital programmes. But he also knows what it means to have cancer. His wife died of it. His sister, mother and father-in-law too. "I have a certain type of cancer myself," he revealed, almost as an aside, during another of his illustrations about how his version of the Dating Agency would work, "and I know where I am, and I'm letting the

industry develop and just kind of waiting to see what happens to my disease. But if all of a sudden I realise I've only got 18 months, maybe I'll take some of my millions and plop it down in the Dating Agency and say, 'I'm going to do that and that', and get the drug real fast. If the mechanisms are in place it can happen pretty quick."

"And there are no such mechanisms in place at the moment?"

"No. Nothing. Nothing even close. What would be really brilliant is to have this agency also include an outreach capacity. There are so many millionaires and billionaires in the world. You're going to have a wealthy Saudi king, you're going to have an Indian maharajah and Silicon Valley billionaires and millionaires – all of them wanting to have access to this. They have brothers and mothers and sisters and, you know, they don't want them to die," he said. And then he repeated it, with genuine compassion and perhaps some fear: "They don't want them to die."

When all other avenues are exhausted, ask your mother.

Ethicists and scientists can afford to have a kindly attitude to excitable writers with no medical training who email them with a new idea about medical funding; lawyers can be less forgiving. I needed a solicitor to pick Lanciano's idea apart. My mother knew what to do. A formidable legal bruiser herself, several years ago she defeated her slimy county council after they failed to act against an illegal shoe factory that had poisoned her with neurotoxins and won £125,000 in compensation. She whispered in someone's ear, who muttered in another ear, and I was put through to Fasken Martineau, one of the world's biggest firms of solicitors specialising in the life sciences, with a particular interest in the law of medical trials.

So far I have seen three partners, who have all shown great kindness and patience in giving up several hours of their time for free because they think the simple Dating Agency idea is both legal and (though said with certain amounts of hand waving and scribbling on pads of paper) "very interesting" – and because, if it got into the wrong hands, it could make someone a *huge* amount of money. They also talked tentatively about what would happen if a commercial element were introduced, in which the wealthy donor would not only secure a position on the trial or a compassionate usage programme, but also purchase a financial stake in the putative new intervention or drug. At this point the Dating Agency would become a capitalist's marketplace, not just a capitalist's last resort – and the complexities and opportunities for fraud and exploitation would blossom. Did I have any business experience? Was I interested in running such a business? they asked idly as they fiddled with their branded pens.

No, on both counts.

And they looked relieved. Lawyers, just like scientists, can be much more humane than you'd expect. It would be better for everyone if this was **run as a charity or nonprofit organisation; it has to be something that everyone trusts, especially doctors.** There would be nothing worse than the Dating Agency getting into the hands of an unscrupulous business with poor scientific oversight, or the hands of woolly, money-wasting do-gooders, and ending up promoting quack medicine.

I will, they very much hoped as they shook my hand in the lobby, beside the coffee table covered in multiple copies of the *Financial Times* and the *Economist*, continue to keep in

touch with them about the progress of the idea. Oh, and though they think Lanciano's **solution is an intriguing one for a biotech company, they think it needs more work before it can also offer the physician sufficient legal protection if the unlicensed drug kills or maims the patient. ??UPDATE???**

Phase three – worth: I talk to scientists

"I think this is a terrific idea," said David Stojdl, a senior scientist at the Children's Hospital of Eastern Ontario and an Associate Professor at the University of Ottawa. Stojdl is a friend of a friend of a doctor I met at a neuroendocrine cancer conference when Dido was still alive. He trained and is a close collaborator with Professor John Bell; together they are regarded as two of the world's leading figures in the hunt for effective oncolytic viruses. (Bell also supports this funding idea, and said he would be happy to consider offering trial places to anyone who funded his work on cancer and was a fully informed and appropriate candidate for testing.)

"Wealthy people already do this," Stojdl pointed out. "We had one individual who came to us with glioblastoma [a form of brain cancer]. He saw our work in the lab on a type of virus that can be injected directly into the tumour or intravenously, was impressed, and wanted to fund us so that he could go on a trial. But the time frames didn't work. It would take us 12 to 18 months to get the trial ready and the drug manufactured up to standard, and he had only six months to live." Stojdl calls this the 'disconnect'.

To get round the disconnect, Stojdl has changed his approach to drug development. By "exhausting" most of the academic, grant-making and philanthropic sources of funding, **Stojdl and his team have almost pulled together the $1 million needed to fund the production of a clinical grade batch of his latest virus, in order that he can have the product in tubes, ready and waiting for when the next rich patient with a brain tumour knocks on his lab door.** "Going at incredible speed" he hopes then to be able to "punch through the logistics of initiating a trial in something nearer to six months". With luck, the patient will also have the sense not to leave things to the last minute, but come early in the disease, before all the usual treatments have failed.

??? HMMM ON WHAT BASIS???
The Dating Agency is no good for people who have already exhausted the established therapies and would willingly sell their house to get a new drug. That's its built-in protection against exploiting the desperation of the poor. It's actually not the desperation of the rich that the Dating Agency uses; it's their gambling instinct.

To take advantage of the Dating Agency (assuming only one person can buy a place on the trial, rather than Professor Savulescu's suggestion that up to half should be allowed to join this way) **you have to be rich enough to be able to put down £2 million for a risky future trial** that you don't yet need and which you know very well might not work; and, to give this gamble any chance of success, you have to do it **just after you've been diagnosed,** when you're still feeling bright and optimistic. As Stojdl's patient with brain cancer found out, **there's absolutely no point in selling your house once the usual therapies have failed, because any new trial you pay for through the Dating Agency won't be able to start in time.** Stojdl's vialled viruses aside, **you have to estimate a minimum delay of at least 12 months,** although that's vastly quicker than any other way of getting hold of new, peer-reviewed medication. If the trial is already running, there's still no need to ring up the estate agents: any suitable patient can then join the trial or get those exemption doses for free.

There are many questions yet to consider.

What about rare diseases for which there are so few patients that it's next to impossible to gather a sufficient number to run a trial except with international coordination? Such diseases (and there are many of them) almost never get new therapies because the trial process is so expensive and difficult to complete.

Recently Dominic and I talked to Cancer52, the charity that represents over half of all cancer patients who die from **less common forms of the disease**. The funding and treatments for such patients can be risible – many do not have any dedicated medications at all because of the weaknesses of the trial process. In these situations could the wealthy patient pay to extend the inclusion criteria of a trial of a drug for a more common cancer, which has a similar biology and is therefore likely to benefit from similar medical approaches?

?? ANOTHER OPP???
This is also relevant to medical interventions, which are often licensed for one complaint, very likely to be effective for another, but only available to the second privately. Regardless of all clinical evidence to the contrary, a lack of bespoke phase III trial evidence allows public health and insurance approval boards to insist that a therapy is not proven to work in unlicensed cases. Such treatments are like the curse of Tantalus to patients without cash. The rich can get them for £20,000, but not the poor. **Could the Dating Agency also help to change this grotesque injustice?**

And if the new trial, which would not have occurred but for the work of the Dating Agency, turns out to be successful and goes to market, **who gets the profits**? Some of them **should be used to promote further research into these underfunded areas of medicine**. But then as scientific researchers can be rotten at business and fluffy about paperwork – and shouldn't be trusted any more than a lab mouse when it comes to setting up trials in the way most likely to lead to a marketable product – should the **Dating Agency include a technology transfer team and also take advantage of the plutocrat's financial nous? The first thing Vince did after offering his money to Uppsala was fly out to the drug production unit and negotiate a 25 per cent discount.**

And what about Peter Lanciano's modification to the Dating Agency proposal? Are extra components needed to make it effective? How can it be translated to the European market, if so? (**There are compassionate usage programmes in Europe, some of which are similar to a Physician IND, but no exact equivalent in the UK.)**

An objection that is sometimes made (especially by clinicians) to the idea of a new funding mechanism for medical research is that the current system does a good job of sorting out good work from the bad. **Because money is hard to come by, it makes it difficult for second-rate projects to get cash. "So the point such people are making is that we've got this sort of natural funding filter," summarises Stojdl, "and the things that are worth pursuing will come to the top, and blah, blah, blah." He pauses for a second, puts his hands together and says succinctly: "That's just bullshit."**

The idea that meanness promotes meritocracy is not just specious, it's crippling – and fatal to people with rare diseases. It's like saying that if you destroy half the rainforest, you'll improve nature because only the fittest animals will survive. "I've seen too many good ideas that don't go anywhere," says Stojdl. "**Sometimes there's political reasons about why**

somebody doesn't get a grant and doesn't get a chance to push their idea forward. Or it might be something as mundane as access to manufacturing facilities. There are only a few academic manufacturing facilities available to produce compounds like viruses to clinical grade, and you might not be able to get into one. Private manufacture is incredibly expensive and oftentimes a disaster. You can build your own manufacturing facility – if you can get grants for that. But **these are not scientific problems, they're structural ones.** My particular *bête noire* is the situation where there are several perfectly good products sitting in one company and you have to pick one because you've only raised enough money to move one on at time. Often, it's just a gut feeling that makes you choose that one over the others. It's not absolute truth. You know you could be wrong."

There are still many questions, **but the Dating Agency idea has got past its three phases of criticism – from ethicists to show that it is not reprehensible, from lawyers to ensure it is legal, and from scientists and biotech CEOs to confirm that it is needed.** According to the current model, once a new medical product has passed the three phases of clinical testing (a process that, for a new drug, typically takes 10 to 15 years and costs around a billion dollars) it can apply for a commercial licence and start to be used at the bedside. So now it's time to offer the Dating Agency up for public use.

Ultimately, the Dating Agency should be run by a reputable, independent and trusted organisation, but, in the meantime, Stojdl has offered to launch the idea using his unlicensed oncolytic virus for adult brain cancer. The details are below. This is the first time in history that clinical trial places have been publicly offered for sale.

I wish, desperately and every day, that there had been something like this up and running when Dido was alive. I might have found out about Uppsala earlier, and got her there on time.

Dan O'Connor is Head of Humanities and Social Science at the Wellcome Trust. Julian Savulescu has received funding from the Wellcome Trust.