1
00:00:01,500 --> 00:00:11,690
Okay. Good afternoon, everybody. And I'm going to tell you a little bit about how new medicines actually become available for patients.

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00:00:11,700 --> 00:00:17,939
So if you like I'm taking some of what Ian has said about the basic research that can be done and give

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00:00:17,940 --> 00:00:23,930
you an overview of how that type of work may eventually lead to a new treatment.

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00:00:24,210 --> 00:00:32,940
And hopefully it will explain to you in a little bit more detail how and why the Centre for Blood Research needs to work together with clinicians.

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00:00:38,270 --> 00:00:43,489
Okay, So what I'm going to talk to you about today are these topics.

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00:00:43,490 --> 00:00:47,990
So I'm going to talk to you a little bit about clinician scientists and,

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00:00:48,230 --> 00:00:52,700
I'm slightly tongue in cheek, because my I need to amuse you as well as tell you facts.

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00:00:53,270 --> 00:00:56,659
I'm going to give you a quick primer on clinical trials,

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00:00:56,660 --> 00:01:06,880
like what actually are they, how they work, what sort of regulation we have governing them, and you know, why they can be tricky at times.

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00:01:07,160 --> 00:01:15,290
And then I'm going to explain to you, if I can, how positive results from clinical trials actually leads to medicines being licensed.

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00:01:15,530 --> 00:01:23,630
And then finally, just a little bit on how the UK decides which licensed medications it's actually going to fund for our population.

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00:01:24,050 --> 00:01:29,420
And each country has its own system of deciding how to do this.

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00:01:29,690 --> 00:01:36,559
So I'm going to tell you about the UK, but it's different in different countries in the world. So I'm going to tell you a little bit.

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00:01:36,560 --> 00:01:41,900
So I'm what's known as a clinician scientist. So I have one foot in both camps.

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00:01:42,440 --> 00:01:47,600
I am clinically qualified, but I also work as a scientist in a lab as well.

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00:01:47,990 --> 00:01:53,510
And I thought about this when I was very newly qualified as a doctor.

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00:01:53,510 --> 00:02:00,830
That gives my age away a little bit. And I had my new bank card, which had Dr. A Fielding on which I was so, so proud about,

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00:02:01,130 --> 00:02:06,800
and I went to pay for some petrol in the garage and the random lady taking payment from me said,

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00:02:08,000 --> 00:02:11,330
Did you get that for being clever, dear, all for being a doctor?

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00:02:11,690 --> 00:02:16,159
And I realised it was a basic distinction.

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00:02:16,160 --> 00:02:21,649
So when people study medicine in the UK it's actually an undergraduate degree and

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00:02:21,650 --> 00:02:25,700
the term doctor when you come out of medical school is actually a courtesy title.

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00:02:25,910 --> 00:02:33,710
So the real doctors are people who have PhDs and they're generally regarded as more clever than people who study medicine.

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00:02:34,580 --> 00:02:39,319
And I understood why. And I may. I thought, oh my God, I need to be more clever.

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00:02:39,320 --> 00:02:46,580
And it was at that time that it occurred to me, that I probably, you know, wasn't at the top of the pile.

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00:02:46,580 --> 00:02:50,660
And I would need to study further in order to better understand things.

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00:02:51,140 --> 00:02:58,100
So clinician scientists or academic clinicians are usually dually qualified in the states they're known as MD, PhDs,

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00:02:58,100 --> 00:03:07,100
but in the UK medicine is an undergraduate degree, so it's a MBBS PhD and in theory they could be great clinicians and great scientists.

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00:03:07,310 --> 00:03:14,360
They focus on one clinical area, they understand the full depth and breadth of that area clinically and scientifically,

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00:03:14,360 --> 00:03:17,000
and they do what Ian referred to, which is translate.

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00:03:17,300 --> 00:03:24,800
So translation is literally and metaphorically because there are certain terms used in science aren't understood by doctors,

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00:03:25,070 --> 00:03:29,660
certain medical terms aren't understood by science. So sometimes that translation is literal,

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00:03:29,900 --> 00:03:34,309
but a lot of it is metaphorical in terms of taking something that's been done in the

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00:03:34,310 --> 00:03:39,650
laboratory and translating it into something real that might happen for a patient.

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00:03:40,220 --> 00:03:45,500
The other way of looking at clinician scientists is that they're dodgy clinicians and under-par scientists.

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00:03:45,740 --> 00:03:49,490
So I see fewer patients than somebody who is a full time clinician.

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00:03:49,850 --> 00:03:53,090
I also have less time to focus on the research lab.

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00:03:53,450 --> 00:04:00,640
I think it's sometimes fair to say that clinician scientists can be less well trained in science than non-clinical scientists.

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00:04:01,040 --> 00:04:08,720
They can be pompous, self-important. And I always think the elephant in the room is we get paid a wee bit more because we also work as doctors.

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00:04:08,990 --> 00:04:15,740
So there's always tensions, you know, as to how these groups of people can work well together.

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00:04:15,950 --> 00:04:19,249
And that's one of the things that attracted me to join York,

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00:04:19,250 --> 00:04:27,709
because some of those important tensions have been sort of dissipated by the whole design of the way the centre has

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00:04:27,710 --> 00:04:34,400
been set up and it's been set up to allow people to work together successfully and not have tensions between them.

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00:04:34,880 --> 00:04:38,120
So I wanted to tell you something else, which I think is quite funny.

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00:04:38,120 --> 00:04:45,440
I once was talking to a very well-known UK based clinician scientist at a dinner,

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00:04:45,620 --> 00:04:51,440
and this guy is very well-known actually, so I'm absolutely not going to name him, but he's now based in the US.

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00:04:51,530 --> 00:04:54,529
And he said, Oh, I just do clinical trials.

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00:04:54,530 --> 00:05:01,340
It's easier than doing basic science. And I thought to myself, you are planning the most complicated experiment,

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00:05:01,550 --> 00:05:08,480
expensive experiment you ever did in your whole life where every single culture or Western blot or whatever he

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00:05:08,480 --> 00:05:14,480
did and all of their relatives can talk to you and ask you for a detailed rationale of what you planned to do.

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00:05:14,720 --> 00:05:20,990
And then you had to tell them all that. And then they had to take their time to decide whether to consent to being in the experiment.

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00:05:21,290 --> 00:05:28,849
Would you think that that was something you'd invest that thought in and less rigour, preparation or insight than you would into a clinical trial?

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00:05:28,850 --> 00:05:31,850
So the answer is no. Clinical trials are science.

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00:05:31,850 --> 00:05:35,780
They're just a different scale of doing science.

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00:05:36,580 --> 00:05:42,460
And they need very careful planning, but there's also a lot of regulation, as there should be, around them.

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00:05:42,820 --> 00:05:46,100
So what is, does anybody, what does somebody,

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00:05:46,390 --> 00:05:49,930
Anybody feel like shouting out what they think is a clinical trial?

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00:05:51,210 --> 00:05:55,650
You don't have to do if you don't want - guinea pig - Okay, That's interesting.

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00:05:55,650 --> 00:06:00,780
So. Right, that's it. So anybody else got any thing they want to shout out about what they first think.

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00:06:04,270 --> 00:06:08,290
Okay. That's one, anybody else? Okay.

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00:06:08,320 --> 00:06:15,010
Right. So a clinical trial is actually defined as any medical research study involving people.

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00:06:16,000 --> 00:06:20,290
And they can roughly be divided into either observational studies.

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00:06:20,920 --> 00:06:23,770
In these types of studies, there are no interventions.

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00:06:24,010 --> 00:06:29,680
So people receive their usual or no treatments or whatever, you know, to the path they're already on.

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00:06:30,190 --> 00:06:38,169
But you can collect data, blood tissue samples, etc. and types of studies that come under.

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00:06:38,170 --> 00:06:46,479
those headings are registry studies or epidemiology studies and what we call post-marketing surveillance,

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00:06:46,480 --> 00:06:49,270
where the drug is already approved and people are receiving it.

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00:06:49,270 --> 00:06:57,610
But you collect data in what we call a real world study or cohort studies, and generally people sign up to participate in these.

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00:06:58,000 --> 00:06:59,530
I'll tell you about that in a moment.

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00:06:59,830 --> 00:07:05,320
Or you can have an interventional study, and that's probably what most people really think of when they think of clinical trials.

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00:07:05,680 --> 00:07:12,250
And in that case, what you're doing is you're testing either a device or a drug or an intervention.

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00:07:12,490 --> 00:07:19,330
So it could even be just an exercise regimen. You know, there are trials where they evaluate whether you have pre-habilitation.

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00:07:19,330 --> 00:07:23,410
You know, you do a certain thing before you have your operation. Do you have a better outcome?

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00:07:23,620 --> 00:07:29,319
There doesn't actually have to be a drug or it could be any form of device, you know, the device you have for delivering insulin.

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00:07:29,320 --> 00:07:37,719
All these things require testing in trials and you're probably aware that there are a number of ways in which things

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00:07:37,720 --> 00:07:44,860
start, so generally they start with pre-clinical laboratory research and that's the sort of thing that Ian was referring to,

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00:07:45,100 --> 00:07:53,469

which currently goes on in the CBR. So there's laboratory research which identifies a new area and generally you do some kind of studies in

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00:07:53,470 --> 00:07:59,020
the lab to determine if you think that treatment's likely to be useful and if it's likely to be safe.

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00:07:59,200 --> 00:08:03,670
And the useful element may just be done on cells or tissues in the lab,

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00:08:04,330 --> 00:08:11,080
some of the early safety data is typically done, as Ian mentioned, in small animal models, usually mice.

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00:08:11,290 --> 00:08:13,990
But there's a big difference, obviously, between mice and men.

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00:08:14,860 --> 00:08:23,950
And you get to a point where the drug is approved for testing in humans and the approval is given by the regulatory authority in the country.

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00:08:23,950 --> 00:08:27,400
So in the in the UK, that's the MHRA.

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00:08:27,820 --> 00:08:31,690
And then typically, if you proceed in a standard way, you have a phase one trial,

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00:08:32,410 --> 00:08:38,470
which is where you're not really looking to see if the drug or device or intervention is going to be effective.

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00:08:38,740 --> 00:08:43,300
But you're looking to see if it's going to be safe. So you'll often start at a dose which is quite low,

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00:08:43,510 --> 00:08:51,070
lower than you think you would need, and work up and generally involves small numbers of people in phase one study so they can be,

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00:08:51,610 --> 00:08:55,930
you know, around 10 or 20 people that would participate in a phase one study.

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00:08:56,140 --> 00:09:01,370
And that will give you some indication of whether, what the dose you can use the drug at, etc.

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00:09:01,390 --> 00:09:08,620
And then you would normally proceed to a phase two study which gives you some more information on safety,

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00:09:08,620 --> 00:09:12,130
but also starts to look into whether the treatment is going to be effective.

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00:09:12,820 --> 00:09:17,110
And phase three studies are generally designed to give you confirmatory evidence.

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00:09:17,350 --> 00:09:20,620
And so oftentimes those studies are randomised,

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00:09:21,130 --> 00:09:30,850
which means that you will be offered the treatment and the other arm will be offered standard of care and normally nobody gets to pick.

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00:09:30,850 --> 00:09:34,419
So 'randomise' means literally by the toss of a coin.

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00:09:34,420 --> 00:09:39,610
So neither the patient nor the physician selects which one of the arms people get.

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00:09:40,270 --> 00:09:49,419
And then once you've completed your phase two studies, you can go on to these once the drug is approved and after the Phase three study,

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00:09:49,420 --> 00:09:56,050
if the phase three study turns out to be positive, that's the point at which you start looking to see if the drug can be licensed.

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00:09:56,410 --> 00:10:01,120
The critical thing about all of this is it proceeds with informed consent.

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00:10:01,390 --> 00:10:05,080
So none of this stuff is ever done to people without their knowledge.

101
00:10:05,830 --> 00:10:12,850
You know, if you're participating in any form of clinical trial and some of you may have done so or known people,

102
00:10:13,090 --> 00:10:18,430
there's a lot of issues because you need to describe as best you can what you're going to do to people.

103
00:10:18,970 --> 00:10:26,500
So the standard to which we practice when we do clinical trials is actually more rigid than the standards applying in normal medical care.

104
00:10:26,800 --> 00:10:30,250
And there's an international harmonisation.

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00:10:30,250 --> 00:10:35,710
So the reason for that is that what happened in the past was that trials would be done in one country,

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00:10:36,010 --> 00:10:41,680
but the data would be considered unacceptable by the regulatory body of a different country.

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00:10:41,890 --> 00:10:46,060
So for example, if we did a trial in the UK and we found a very,

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00:10:46,060 --> 00:10:54,760
very positive result, nonetheless the trial would have to be done again in the United States because the United States Regulatory Authority,

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00:10:54,760 --> 00:11:01,870
the FDA, wouldn't accept the data from the UK. So some years ago people thought that that was stupid because it is stupid.

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00:11:01,870 --> 00:11:07,240
So now there's very strong international regulation so that wherever

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00:11:07,440 --> 00:11:13,500
the clinical trial is done in the world, done to the exact same standard, and the standards are very high.

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00:11:13,860 --> 00:11:21,780
So there are very tight guidelines on the ethical and practical conduct of a clinical trial, and the rights of participants are paramount.

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00:11:22,050 --> 00:11:29,880
But it's also critically important that the data that you get are authentic, credible and valid across international borders.

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00:11:30,150 --> 00:11:34,770
So when we collect data in clinical trials, it's done to a very rigid standard.

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00:11:35,040 --> 00:11:42,780

So there's comprehensive documentation and constant monitoring and inspections, to make sure that the data you've got are accurate.

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00:11:43,380 --> 00:11:51,630
And this means that when you get the outcome from a clinical trial, you haven't wasted the time of any person who's consented to participate.

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00:11:52,620 --> 00:11:55,050
So, what do you need to do a clinical trial?

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00:11:55,380 --> 00:12:03,750
So you need, obviously a drug, device or an intervention worth testing or perhaps a rare condition where you want to collect data and specimens,

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00:12:03,750 --> 00:12:08,880
but you need a bloody good reason to do one because it's time consuming and expensive.

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00:12:09,360 --> 00:12:14,490
So you need a sponsor who is legally responsible for the conduct of the study.

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00:12:14,850 --> 00:12:20,700
So sponsors are most often universities or hospitals,

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00:12:21,240 --> 00:12:27,780
but they're the people who are going to end up in prison if something is done wrong.

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00:12:28,290 --> 00:12:29,819
You need a chief investigator.

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00:12:29,820 --> 00:12:38,970
It's usually somebody who's clinically qualified who is personally responsible for overseeing many aspects of the conduct.

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00:12:39,330 --> 00:12:40,620
You need ethical approval.

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00:12:40,620 --> 00:12:47,579
So you need to go to one of the many national ethical committees that we have to say that what you're planning to do is appropriate,

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00:12:47,580 --> 00:12:54,090
and what you're telling participants and what you're asking of them is not too burdensome, is considered reasonable.

128
00:12:54,510 --> 00:12:58,379
You need national regulatory body approval of what you plan to do.

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00:12:58,380 --> 00:13:01,840
In this case, it's the MHRA. You need sites,

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00:13:01,860 --> 00:13:06,990
So usually the types of trial I work on, they're usually sites in the NHS.

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00:13:07,320 --> 00:13:14,730
They can be GP practices, they can be hospitals. In my context, it's usually hospitals who treat patients with the disease that I'm interested in.

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00:13:15,060 --> 00:13:22,890
They need to be able to recruit patients to the trial, provide appropriate care, provide the data in the format that's required,

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00:13:23,100 --> 00:13:29,040
and each site needs to have its own lead investigator who's responsible for the study at that site.

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00:13:29,370 --> 00:13:35,760
So as you can imagine, putting all that together is quite expensive, it's time consuming,

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00:13:36,480 --> 00:13:43,290
and you have to pay attention to many other things, such as the storage of tissues and access.

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00:13:43,290 --> 00:13:48,029
You know, if somebody takes blood from you and stores it in a biobank, it will have taken,

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00:13:48,030 --> 00:13:52,260
believe you me, about a year to get the consent and regulatory stuff up for that.

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00:13:52,710 --> 00:13:55,740
If you're doing anything with a novel genetic therapy

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00:13:55,740 --> 00:13:59,250
there are certain rules on that. There are rules on radiation exposure.

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00:13:59,250 --> 00:14:04,920
So even if you have a chest X-ray in a clinical trial, you know, the dose has to be calculated, is it fair.

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00:14:04,920 --> 00:14:08,910
So there's a lot going on. And of course, it generates an enormous amount of paperwork.

142
00:14:09,480 --> 00:14:15,330
So you need to be really determined and have a really good plan in order to go through all of this.

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00:14:16,290 --> 00:14:24,329
The role of a chief investigator is taking overall responsibility for the conduct and communicates really between the sponsor,

144
00:14:24,330 --> 00:14:29,730
the ethics and all these bodies, whereas the principal investigator, there's one at every single site.

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00:14:30,000 --> 00:14:36,090
So if you're invited to participate in a clinical trial, there'll be somebody supervising the trial at your site,

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00:14:36,240 --> 00:14:42,300
and there will also be somebody nationally who's supervising the whole trial across all of the sites.

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00:14:43,590 --> 00:14:48,270
So how do trial results lead to medicines being available for patients?

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00:14:48,510 --> 00:14:53,070
So essentially we have what we call regulatory approval, which means a licence,

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00:14:53,400 --> 00:15:00,150
so you can market, sell or purchase a medicine if it doesn't have a licence.

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00:15:00,540 --> 00:15:09,150
So marketing authorisation is the process of reviewing and assessing the evidence to grant your product a licence so it can be sold.

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00:15:09,870 --> 00:15:11,999
And the licence is very specific.

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00:15:12,000 --> 00:15:19,620
So it will state exactly which illness the medicine can be used for, how much can be given and what group of patients it can be given to.

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00:15:19,770 --> 00:15:26,430

So for example, if the medicine has only been tested in adults, it can be tricky to prescribe it in children,

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00:15:26,700 --> 00:15:32,960
if the medicine has only been tested in disease X, it can be very difficult to prescribe it in disease Y.

155
00:15:33,630 --> 00:15:37,200
And the licence is provided by by a government organisation.

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00:15:37,620 --> 00:15:42,029
And going for a licence requires a lot of very careful orchestration.

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00:15:42,030 --> 00:15:47,609
And generally it's the owner of the company who goes for the licence, so the owner of the product.

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00:15:47,610 --> 00:15:55,770
So it's generally the drug company. Individuals such as myself are not capable really to go for a licence.

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00:15:56,430 --> 00:16:00,110
So how long do you think all this takes? Well, it takes a long time.

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00:16:00,120 --> 00:16:06,330
So the early bit of the drug discovery can take place over many years.

161
00:16:07,310 --> 00:16:13,639
It can take a long time to set the trials up, to get the marketing authorisation.

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00:16:13,640 --> 00:16:17,000
So you can see that you're accumulating enormous amounts of time

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00:16:17,280 --> 00:16:23,540
from when somebody first has a good idea to when something might end up as a tablet in your medicine cupboard.

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00:16:24,020 --> 00:16:27,350
So why does it take so long? So there's a couple of things.

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00:16:27,360 --> 00:16:31,060
So when you have this, we have this thing called the Valley of Death.

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00:16:31,070 --> 00:16:36,979
So people have great ideas in the lab at the point of translational science.

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00:16:36,980 --> 00:16:42,070
where it looks like it's going to be really good. It's very, very hard to get things to clinical trials.

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00:16:42,080 --> 00:16:45,950
as I've just explained because you need a whole lot of stuff to work out,

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00:16:45,950 --> 00:16:52,220
right, and a lot of money. So a lot of very good ideas in the lab never actually make it through to clinical trial.

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00:16:52,820 --> 00:16:56,719
And then there's a second, what we call the second valley of death, for new medicines,

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00:16:56,720 --> 00:17:01,100
and that's between phase three clinical trials and adoption into clinical practice.

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00:17:01,520 --> 00:17:07,430
So even if the medicine has been shown to be successful in a randomised phase three clinical trial,

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00:17:07,700 --> 00:17:13,579
it still needs to go to the MHRA for approval, and then it still in the UK needs to be approved by NICE,

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00:17:13,580 --> 00:17:18,920
which means it's going to be paid for as a medicine that you can receive prescribed by your doctors.

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00:17:19,430 --> 00:17:24,409
And there's big gaps there, you know, and the reason for these gaps is manyfold.

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00:17:24,410 --> 00:17:31,340
But some of them are, if I'm an academic and I have a medicine and I am lucky enough to test it in a Phase three clinical trial,

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00:17:31,850 --> 00:17:34,219
I can't change the licence for that product.

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00:17:34,220 --> 00:17:44,570
So say I do something amazing, like I discover aspirin, not aspirin because it's off patent, but some drug unexpectedly cures leukaemia.

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00:17:45,050 --> 00:17:49,850
If the company don't want to change the licence for that drug, there's nothing I can do about it

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00:17:49,850 --> 00:17:56,450
as an academic investigator. And some companies don't want to pursue licence changes because it costs a lot of work and money.

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00:17:56,720 --> 00:17:59,570
And if there's not a lot of patients that have that condition,

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00:17:59,810 --> 00:18:03,650
they won't necessarily be bothered even though the medicine is potentially effective.

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00:18:04,310 --> 00:18:10,720
So many countries don't approve off licence prescribing, so the UK tends to be one of those countries.

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00:18:10,730 --> 00:18:18,590
So if you live in the US and you've got good insurance and plenty of money, you can get pretty much any medicine that's licensed for any condition.

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00:18:18,590 --> 00:18:25,129
But in the UK and many other European countries you can't do off label prescribing and a drug with a positive

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00:18:25,130 --> 00:18:29,450
trial outcome may be so expensive that even though it's given a positive outcome,

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00:18:29,450 --> 00:18:33,770
is too expensive to be afforded on a large population basis.

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00:18:34,490 --> 00:18:39,050
So licensing doesn't automatically mean it's going to be available for you as a patient.

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00:18:39,350 --> 00:18:46,009
So who's footing the bill? And in the UK we have the National Institute for Health and Care Excellence that

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00:18:46,010 --> 00:18:50,570
reviews each treatment and bases their decision on the best evidence.

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00:18:50,840 --> 00:18:56,120
And they don't just look, is the medicine effective? They also look, is it economically effective?

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00:18:56,390 --> 00:19:02,120
So they they use something called quality adjusted life years to assess the potential benefit,

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00:19:02,660 --> 00:19:09,290
not just in terms of is a person alive or not alive, but also in terms of what their quality of life is.

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00:19:09,560 --> 00:19:19,580
So if a drug has an enormous benefit in improving somebody's quality of life, even though it's very expensive, it can still potentially be approved.

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00:19:20,030 --> 00:19:27,950
And NICE does take input from as well as from experts, from lay members, clinical, public, all sorts of stuff.

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00:19:28,190 --> 00:19:30,379
So there's a lot of public involvement in NICE.

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00:19:30,380 --> 00:19:37,630
And if it's something that you're interested in, I'd strongly encourage you, you know, to get involved in participating.

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00:19:38,210 --> 00:19:46,970
So that was all I wanted to tell you today. But I just hope that I've explained to you that the presence of clinicians and clinician scientists at

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00:19:46,970 --> 00:19:53,420
York helps us to be committed to working together as a team to learn about the science of blood cancers,

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00:19:53,990 --> 00:19:58,160
to develop and test new treatments and improve the outcome for patients.

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00:19:58,400 --> 00:20:04,070
So we do epidemiology, basic science, clinical science, and it's for patients.

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00:20:04,610 --> 00:20:07,550
So thank you for your attention and happy to take questions.