The secret behind a successful clinical trial

Pinuccia Valagussa shares the insights gained from 40 years at the helm

➜ Simon Crompton

Good clinical trials are proposed by clinicians, have the potential for real patient benefit and increase knowledge about the disease. So says **Pinuccia Valagussa**, who forgets to mention another secret of success: having someone like herself in charge, who works closely with clinicians, keeps tight control over the quality of data, and is dedicated to helping more and more centres join trials.

The first thing that Pinuccia Valagussa says to me when I meet her in the reception of the Istituto Nazionale Tumori in Milan is that she doesn't want to do this interview. This is a little disconcerting, though she says it in a very friendly, polite manner. Then, thank goodness, she leads me down the corridors to her office, explaining that of course she will do it, so that she can get over important messages about clinical trials and current barriers to good research. It's just that the more she's thought about the interview, the more she's feared it.

The problem is that Valagussa, a woman who has been at the centre of some key trials in the recent history of cancer research, hates talking about herself. She agrees to interviews thinking it flattering, but then has second thoughts because, she says, she is a very private person.

Her dislike of the limelight isn't affectation. During most of our interview, Valagussa, who is director of the Operations Office for Clinical Trials at the Michelangelo Foundation in Milan, speaks openly and animatedly – discussing the qualities of good trials, the bureaucracy that stifles significant research, and some of the exciting studies she has been involved with over 40 years. She is all expressive hands, facial contortions and a combination of both that makes Italians uniquely able to express "that's how it goes", "what can you do?" and "I told you so" all in one go.

Yet when I venture into her background, motivations and influences, all that stops. "I really don't know what to tell you," becomes a regular reply.

Her demeanour is perhaps not unexpected given that she has had a central role in 350 papers on systemic adjuvant therapy for early breast cancer, treatment of malignant lymphomas and methodology in clinical trials, yet her name has rarely been first in lists of authors. Valagussa may be a lynchpin to some of the major advances in clinical oncology over four decades, and she may have received several awards (including an Italian Woman of the Year Award in 1997 and a City

ELIGIO PAONI

of Monza scientific merit award in 2005), but she works in the background.

She has run the Operations Office for Clinical Trials at the Istituto Nazionale Tumori in Milan since 1973, seeing its clinical trials office develop in 1999 into the Fondazione Michelangelo, a non-profit organisation devoted to advancing research in cancer. In 2007 she became a director of the foundation. The office where she has worked since the start is in the old part of Istituto Nazionale Tumori. The walls are covered with prints of impressionist paintings – the choice of renowned cancer doctor Gianni Bonadonna, who founded the Michelangelo Foundation. Despite having had a disabling brain haemorrhage in 1995, Bonadonna is still the heart and soul of the operation: his book-smothered office is next to Valagussa's, and he greets me warmly with a left-handed hand-shake.

Dedicated to clinical trials

Valagussa explains to me how the principle aim of the Michelangelo Foundation is to design and conduct clinical studies and translational research. Free of charge and independently, it assists clinical oncology investigators from the earliest planning stages. "We go through all the administrative burden, ask other sites to join the investigation, discuss the objectives and scheme of the study, go to the regulatory authorities and ethics committees, collect all the data, assess the quality of the data, plan and conduct the analysis, and prepare for presentation and publication."

The rigour the foundation applies to planning studies assures a quality of research that is far more likely to have an impact on clinical practice and patient care than studies that are poorly designed or never get off the ground because of

time-consuming administrative procedures. Valagussa's office ensures that nothing coordinated by them compromises its high standards.

"A good clinical trial is first of all one that is proposed by clinicians, because they have ideas. The hypothesis, if proved, must show a benefit that is clinically important and important to the patient. For example, is it important to start a very large study with the aim of finding a difference of no more than 3% between treatments *a* and *b*? You may improve the rate of survival but a new treatment may also have risks. There's a danger that such studies are like comparing Coca Cola with Pepsi Cola: is the goal really to benefit the patient?

"A good clinical trial improves knowledge of the disease, and it is important nowadays that when designing a clinical study you have to keep in mind that you will need to correlate it with a translational study. So you need to talk to your patients and explain the importance of them donating samples for future research."

Outstanding young investigator 1985. Valagussa's contribution to setting up some of the first big breast cancer trials was recognised with this prize awarded by the Italian Health Minister

An impressive track record

The research that Valagussa and her team have been involved in over the decades demonstrates the potential impact of well-planned clinical research. In the early 1970s, with Bonadonna, she coordinated the landmark trial showing that adjuvant CMF (cyclophosphamide, methotrexate and fluorouracil) provided significant survival benefits for women with operable breast cancer – a finding that has been confirmed in follow-up studies over 30 years. "It was quite a departure. We demonstrated to surgeons how patients could be cured with chemotherapy, so it began to change mentalities, and was the beginning of the multidisciplinary approach."

Another landmark trial occurred in the early 1970s, when Bonadonna designed a new combination chemotherapy for Hodgkin's disease known as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine). With Bonadonna, she coordinated the trial that in 1974 showed the superiority of ABVD compared with the standard MOPP (mecloretamine, vincristine, procarbazine, prednisone) chemotherapy. ABVD is today still considered the gold standard for conventional chemotherapy in Hodgkin's disease.

In the late 1980s, she coordinated trials under Bonadonna and with the support of Umberto Veronesi, which challenged the classic indication of mastectomy for breast tumours of three centimetres or more, demonstrating that primary chemotherapy before surgery reduced tumour size, and that conservative surgery could be an effective and safe alternative to radical surgery. "In what was, and still is, a surgical centre, we were able to say: 'Please, now, we can all help our patients preserve their body integrity by starting

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"We can all help patients preserve their body integrity by starting with chemotherapy followed by surgery"

with chemotherapy followed by surgery.' It took a while to convince people, but we managed it."

There's much more to come. She is currently planning a global trial of a new type of adjuvant therapy, involving groups from Italy, Britain and Australia, but the details as yet have to be kept under wraps.

There have been massive changes in the scope of trials into cancer drugs over the four decades that Valagussa has been at the Istituto Nazionale Tumori. She first came in 1969, a Red Cross volunteer nurse based at Monza Hospital attending a cancer course that the Institute was holding. Because she had studied languages at high school, spoke English and had attended courses in statistics while in Monza, she was asked by Veronesi to join the Institute as a scientific secretary.

"Nobody really told me what they wanted from me until my first day in the job, when Professor Veronesi told me I would be involved in trials. I didn't know what this meant. I never associated the word trial with medicine before."

Soon she was thrown into compiling information for Veronesi's trial on breast cancer surgery, and typing up Bonadonna's protocols for chemotherapy trials. The clinical trials operations office, officially set up to concentrate on medical oncology in 1972, was originally a small affair. It coordinated only single-centre studies for the Institute itself and had just three staff. Now there are 12 staff, coordinating studies in 35 centres around the world.

Going multicentre

Its growth can be traced to 1993, when Bonadonna decided to respond to requests from medical oncologists whom he had trained, and were now working elsewhere in Italy: they wanted to participate in some of the clinical studies he was running. "It was with some reluctance initially," says Valagussa, "because you are used to working within your own group, and it's not that easy to change. But it was an important step, because it meant we would be able to cooperate together according to certain rules, and it would allow patients from other regions of Italy to have good experimental treatments, based on sound clinical reasoning, without coming to Milan."

So around 15 medical oncologists from northern Italy got together for an exploratory meeting at the Michelangelo Hotel near Milan train station; they decided to stay in touch, and called themselves the Michelangelo group. They did indeed start multicentre trials, coordinated from the trials office of the Istituto Nazionale Tumori, and years later, when the work of the office became formalised into the new foundation, Bonadonna decided to continue with the Michelangelo name.

The move to international multicentre trials came in the mid 1990s, when Bonadonna was designing a new randomised trial to test classical adjuvant chemotherapy against neoadjuvant primary chemotherapy before surgery in cases of moderate- to high-risk breast cancer. One of the drug companies providing funding asked whether it would be possible to conduct it as an international trial. So a protocol was

A phenomenal partnership. The collaboration between Valagussa and Gianni Bonadonna, one of medical oncology's great leaders, has not just improved survival and quality of life for countless cancer patients but helped set the standards for clinical research

arranged and plans were made. And then Bonadonna had a brain haemorrhage.

"We had a big discussion in Paris with the investigators and the drug company, and we had to ask whether we could continue this adventure without Dr Bonadonna. Finally, Professor Luca Gianni, then director of medical oncology at the Istituto Nazionale Tumori, accepted the challenge. So in 1996, we started the internationalisation of our foundation. And once we did it, we knew we could do it again and again."

International trials suddenly presented Valagussa and her colleagues with new challenges for organising consistent protocols. Different countries had very different perceptions of what 'best conventional treatment' was. There were different technological levels – some centres participating in trials in the late 1990s did not even have routine access to the internet. Drug companies funding the trials had to be asked for more money to help less well-resourced sites participate.

Achieving quality data in these large trials is time consuming. "It's costly, but not just financially. It's not always easy to get investigators to send the right kind of data at the right time – they have their job to do in their clinic, after all. And you need to convince them of the importance of following rigorously all the safety procedures in your protocol. And if something doesn't look right to you in the data, you need to call the investigators and discuss it with them and provide advice. What qualifies our team is the clinical quality of the data. While the main priority of a drug company might be to ensure that all the right boxes in the study have been filled, and this might be done at the end of a study, our emphasis right from the start is to check the quality of the data. It's not so important that information is missing. It's important that what you have is good."

The burden of bureaucracy

But the biggest challenges have always been posed by bureaucracy. It's a problem that afflicts researchers in every country, but Valagussa believes international trials are battling against almost impossible odds to get off the ground. Even a specialist trials office such as her own struggles with the convolutions of red tape that drain time and money. If all goes smoothly in planning for a large study, it will take at least four years to complete enrolment and many more years to follow-up. In that time, other findings and developments may have made a study's original objectives obsolete. Valagussa says the situation is sometimes "nightmarish" for organisations like her own attempting independent research driven by the needs of patients.

"The regulatory authorities are all different in every country involved. You have to get your protocol cleared with them, and then present to the ethics committee, and then you have to select the participating sites. Nowadays, things are getting worse. For example, for a non-profit organisation like ourselves, conducting a non-profit study, it is not clear under European rules whether you, as the sponsor, have to pay for the drugs used in the study, even when they have been registered for the indicated use. It seems to be different in different countries.

"According to European regulations, sponsors have to provide a fee to the regulatory committee and a fee to the ethics committee. They often have to pay for all the drugs, and sometimes for extra patient examinations. If this continues, what is the future possibility of academics and institutes like our own conducting studies? They are just too expensive."

So it is inevitable that funding from commercial sources has to be accepted for many studies. Valagussa's office tries to help researchers find independent sources of funding, but these rarely cover the full cost of a study. Since much of the research is to establish new indications for drugs that have already been approved, drug companies are asked for support too. But Valagussa emphasises that there can be no drug company intervention in studies' design or objectives.

What could be done to make quality, independent multicentre research easier to accomplish? Valagussa shakes her head wearily. "I haven't any idea. We do need rules, and people to apply them, for the good of patients and the studies themselves. Years ago, we had few regulations, and

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that was wrong. But when you go to the bureaucrats, you always seem to be fighting a losing battle. You ask them, 'What do these words mean?' They have one interpretation. I have another. A third person has another. What can you do?" She tentatively suggests that one central European committee might help, so that separate authority wouldn't have to be sought from regulators in each country: but EU regulations are not famous for their clarity.

It's about patients

Despite all this, Valagussa is a great believer in international, multicentre trials. They bring benefits to a far larger group of patients than single-centre studies. "I think you have to believe you are doing your best for patients, and to share the options you have for treatment in your country with other countries. More patients benefit if you have several sites, working as if they are one specialised centre. You get a good exchange of information between investigators, and the focus is on improvement."

The patient, she emphasises, should drive everything. It's important to work with them before, during and after trials, often through patient organisations. User input into the design of consent forms is particularly important, she says. It is too easy to design consent forms that only clinicians understand – and even they sometimes find them difficult.

I wonder whether her background as a nurse has helped provide a patient-conscious counterpoint to the perspective of doctors in designing trials. She shrugs. Not really, she says. And as we begin to touch on her personal contribution and qualities, the answers begin to dry up. I learn that she is single, sees a great deal of her 10 nephews and nieces, and their 10 children, and likes travelling, reading thrillers and listening to classical music. But she doesn't wish to go into details about what makes her tick. "If you let me talk about protocols, that's fine. Otherwise, I stay quiet."

An internationalist. Valagussa goes out of her way to help new countries and new institutions participate in multicentre trials, even though this complicates her task of controlling the quality of the data collected. She is pictured here at a regional breast cancer conference in Uruguay, 1999

Actually, what motivates her has become obvious as we talked about her work, and about the debt she feels to Bonadonna for his confidence in her since her earliest days at the Institute. "I've always appreciated that I've been able to talk openly with all the clinicians I've worked with – just sensing that we were, and are, a team, working together out of scientific curiosity. We all have this same challenge ahead of us, framing the clinician's perspective in the right way so that we can test what we think according to the correct methodologies."

And sometimes, when the hard data show something really exciting, the shy person who wants to keep the personal out of the professional can't help acknowledging her personal investment in the work. "When you start a study, your main priority has to be not to harm our patients for the sake of a scientific idea. But when you get the initial results, sometimes you cannot help being excited. You get a leap inside, and say: yes, we are on the right road. We have not solved it, but we are on the right road."