ICPV Clinical Trials Course – Warwick Medical School, University of Warwick: 17th-19th April 2018
Course Report

This 3 day workshop on Clinical Trials was put together for ICPV by Professor Janet Dunn at Warwick University. Previously, this has been on the programme of the ICPV VOICE Courses – Science for Patient Advocates http://www.independentcancerpatientsvoice.org.uk/voice-science-for-patient-advocates/ but ICPV members who had attended the VOICE course found the subject to be too important to be taught effectively in such a short time. So it was decided to run this workshop exclusively for the subject and for ICPV members. If successful this workshop could become a permanent extension of the VOICE course, offered to patient advocates as part of a repertoire of educational courses.

Prof Janet Dunn was in overall charge of the teaching and was instrumental in putting the programme together. Sophie Gasson and Lesley Turner facilitated the course. 12 ICPV members took part, most of whom had previously attended a VOICE Course. The workshop was residential with accommodation and most of the teaching at Radcliffe Conference Centre, Warwick University.

The course was jointly funded by ICPV and Warwick CTU with all teaching provided by Warwick CTU.

Day 1: Types of studies, evidence and consent

Session 1 – Case Control, Cohort and Clinical Trials – Janet Dunn

The workshop began with an introductory session on types of studies, evidence and consent. The objective was for all the students to gain a broad understanding of the types of studies which are conducted. Historical examples were given to illustrate the progress and advancement of research.

The pace was quick with a lot of information to be given. The session was interactive and discursive with all students getting involved. No question was considered too menial.

Feedback was positive. There was a range of background knowledge among the students, some with very little knowledge and experience of clinical trials:

- *'All of it was pretty new for me!'*
- *'Case control is something I knew little about.'*

Others had more extensive experience:

- *'Revised my understanding of different study types.'*

Despite this range, all students reported having learned a great deal:

- *'We covered an awful lot so I know a lot more than I did. I was familiar with the terminology but to be able to put it into practice is another matter. More time and practice will be needed.'*
- *'Epidemiology landmarks were really interesting.'*
- *'Raised my awareness of the no of decisions that need to be taken before proceeding.'*
- *'Some aspects of bias and risk opened my eyes to new thinking.'*
- *'I hadn't really appreciated the intricacies of cohort selection and definitions.'*

With some surprises:

- *'Had not previously thought of trials as population studies and thus epidemiology.'*
- *'Epidemiology brings other problems!'*
- *'I also found out about the Government's priorities for research.'*

Clinical Equipoise was a term new to many students and which Janet explained clearly:

- *'Hadn't come across 'Clinical Equipoise' as a term before but had/do understand that best treatment is not always known.'*

Students were asked whether there was anything they'd like to know more about and offered the following:

- 'Bias.'
- 'Time for more examples – these are so helpful and interactive.'
- 'How to design a blob-a-gram.'
- 'Perhaps some basic rules for deciding cohort selection.'

Session 2 – Understanding evidence – Janet Dunn

This session covered systematic reviews – an overview of why and how they are done. The necessity of conducting these reviews was explained along with an historical account of how this evolved. Students were told about Cochrane reports and where they fit in.

Feedback was positive and suggested that participants grasped the principles of systematic reviews:

- *'It was good to be reminded about the different levels of evidence and that a systematic review of randomised trials was the gold standard.'*
- *'I didn't know how long it took to establish that there is 'no alternative' to doing a systematic review.'*
- *'I'm now clear about negative aspects of narrative review and positive aspects of systematic review.'*
- *'I didn't realise that Cochrane was about 18 moths out of date in terms of research evidence.'*

Students were asked whether there was anything they'd like to know more about:

- *'Results from systematic reviews may be limited by quality of included evidence and other issues – more about how to avoid/reduce the risk of this.'*
- *'I would have liked more information and more time on forest plots etc.'*
- *'Inclusion bias.'*

Session 3 - Trial summaries and Patient Information Sheets (PIS's) – how do we understand what the trial is all about? – Janet Dunn

Trial summaries and information given to patients to help them decide whether or not to take part are very important. Reviewing these documents is an important part of the work done by ICPV in partnership with researchers. In this session, summaries and PIS's from several different trials were examined and the students were encouraged to think about the efficacy of each one.

Students found this session to be informative, benefiting from the practical and interactive aspect of it:

- *'ICPV participants always gain much from practical sessions and ask thoughtful questions and contribute well to discussion.'*
- *'Useful to see some different information sheets, good and not good examples. Confirmed some of my thoughts about information sheets, how to make them user friendly.'*

In a future course, this session may benefit from a longer time slot:

- *'Needed more time for the practical session really. Might have been better if we had had the papers to read through beforehand.'*
- *'It was a good learning experience – I think the timing should be less rushed if it's repeated on another similar course.'*

Session 4 - Practical: Role-play informed consent

Informed consent is another important aspect of ICPV's PPI work. Members are often asked to review Informed Consent forms (ICF's) to help ensure that they are understandable and accurate. This session was designed to enable the students to see taking informed consent from the researchers or clinicians perspective and to give them an idea of how involved the process can be in an often busy and over-subscribed clinic situation:

- 'Very useful as a practical session – helped to see that some additional, helpful information is missing. We couldn't imagine working through this informed consent in less than half an hour.'
- 'I really enjoyed having this as a practical session. It is a very good way to fully understand how difficult it is to ensure that the patient is fully informed without pressurising the patient to agree to the trial. It takes a lot of listening skills and patience to be really effective at this.'
- 'It must take a long time – no idea how they fit these discussions into 30 mins.'

Role play can be challenging for many people but the students embraced it and learned a great deal from the session:

- *'More difficult than I thought in trying not to unduly influence the patient/participant, particularly when needing to indicate the importance of research but maintain equipoise about the particular study or trial.'*

As with the previous session, more time would have been beneficial and perhaps more space to work in:

- *'It was rather rushed time wise and the noise level of others voices (which wasn't very loud) nevertheless detracted from the sort of environment I would expect to be in when this would be discussed with a patient.'*

Day 2: Design, Analysis and Interpretation

Session 1: Introduction to Clinical Trials & Trial Design -1

This first session aimed to give students an overview of trial design and some insight into how the many different types of design can be utilised effectively to try to answer the research questions. Systematic reviews were also explained and were new to many of the students. There was a huge amount of information given in this session - students were asked what they learned:

- *'Phases of trials – how the studies advance from small cohorts in phase 1 to phase 2 and 3.'*
- *'Learned what 'intention to treat' means.'*
- *'That the results of any study are only really an estimate and that we should be very wary of small numbers in trials.'*
- *'That the inclusion of studies into trials are subjective, and negative results are not always reported.'*
- *'To always think about bias.'*
- *'To always do a systematic review.'*
- *'I didn't know about the different trial designs – parallel, crossover, factorial design. I've seen examples in various protocols but hadn't needed to know how, why and when to use them.'*
- *'Why phase I and II trials are often done at the same time and how they can be combined.'*
- *'Factorial design to enable more than one question to be asked.'*
- *'Dose expansion.'*
- *'That it is possible to go direct to a drug company for the results of a trial that might not be reported anywhere else.'*

The use of placebos was discussed – their importance and their cost. The cost was a revelation to many of the students:

- *'Costs of producing placebos and need to manufacture active placebo side by side even if active drug is cheap and readily available.'*
- *'No awareness of potential huge costs for placebo. Always assume costs for all non-placebo drugs.'*

Session 2: Practical – trial design – Janet Dunn

A practical session was included to give the students the opportunity to try to design a trial which could potentially answer a research question. Examples of existing research questions were given and the ideas the students came up with were then compared with the actual trial designs. Feedback from this session was mixed with the message that the format was suitable:

- *'Wasn't what I was expecting which was to have a go at designing a study but when we did it I enjoyed it although we had too little time – very helpful to try to apply the learning from earlier.'*
- *'It helped understand trial design more deeply.'*

But that more time would be needed to benefit more fully from this type of practical session:

- *'Really needed a lot more time to do this. We achieved very little in the time we had. It was useful to see how much information is needed before designing a trial.'*
- *'However, I thought this was a great session and that we could have done with more time to review all the trials.'*

Session 3: Trial Design 2 and Trial Analysis – Janet Dunn

Statistics! This was the session which had been requested many times over – ICPV members have long felt they needed some teaching on statistics to enable them to better understand how the results of clinical trials are analysed. A huge amount of information and many new concepts were included in this session. Some felt the information was too much to take in and some felt that more time was needed to explain all of it well. However, a great deal of learning took place with students reporting having learned the following:

- *'Hypothesis, power calculations, p-value etc. Now have a better understanding of, for me, a complex subject and also excellent notes to refer to.'*
- *'Considering the cohort and all the other elements that need to be prepared/accounted for!'*
- *'Clarified meanings of many terms but a lot of information and quite a reasonable level of knowledge needed to follow it all.'*
- *'The best designed trials are prospective.'*
- *'Phase 1 to 4 trials are just for cancer patients. Healthy volunteers are different.'*
- *'When you analyse results you should think about "dropping the loser not picking the winner".'*
- *'Cluster randomisation trials are usually GP trials.'*
- *'The Zelen method is not a great way to randomise.'*
- *'Null hypothesis = no treatment difference.'*
- *'A lot of new terminology.'*
- *'I had never heard of the EQUATOR network before.'*
- *'Graphical display of results.'*

- *'After hearing about the null hypothesis at school about 55 years ago, I now know it is used for modern statistical methods to establish sample sizes and the relative significance of data in clinical trials!'*

Session 4: Bringing a drug into market - case study – Hema Mistry

Hema explained how once a trial is completed, a drug is brought into market. Hema explained the potential difficulties which can be encountered along the way and described the role of NICE:

- *'I knew nothing about the NICE process before this so learned about how it works with a good example to illustrate a wide range of issues.'*

and the Evidence Review Group (ERG):

- *'I knew nothing about the work of the Evidence Review Group before this session. It was an interesting session and useful to have included this in the course.'*

Most of this was new to the students who reported having learned the following:

- *'How random the whole process is!'*
- *'That there is a cost-effectiveness analysis done independently.'*
- *'That there are different cost thresholds for cancer drugs etc.'*
- *'This reinforced some of the experiences trials I am involved with are having – I learned a lot about the possible reasons for this.'*

There was a lot of discussion around the difficulties encountered during the process which evoked some strong feeling among the students:

- *'What a waste of money NICE seems to be – based on what we heard– they might as well cut out all the so called 'evidence' and admit it's down to who shouts the loudest (or – dare I say – who says what to who…?)'*
- *'The Government moves the goal posts....'*
- *'I find this subject upsetting and I get angry knowing, when it comes down to it, a person's life has a monetary value put on it.'*
- *'Scientific rigour and statistical analysis do not necessarily overcome Pharma financial resources!'*

Based on this session, if more time were available the students would like to learn more about the following:

- *'QUALYs and the nitty gritty of how cost and effectiveness are calculated.'*
- *'How the decisions are actually made and the roles patients and carers can play in that.'*
- *'More about the whole NICE process and not just about the evidence validation.'*
- *'How NICE decides new very expensive equipment is cost effective – e.g. Proton beam therapy.'*
- *'…evidence of a positive outcome of ERG work.'*

Day 3: Anatomy, non-drug trials and dissemination of trial results

Session 1: Anatomy visit at UHCW – Dr Jamie Roebuck

UHCW holds a complete collection of plastinate anatomical specimens which are used for teaching: https://warwick.ac.uk/fac/med/study/ugr/courseinfo/facilities/#anamtraining. This session was arranged to give the students a unique opportunity to see and handle the unique specimens and to learn from the dedicated demonstrators in the Surgical Teaching Centre. Jamie Roebuck led a team of anatomy demonstrators and medical students to deliver a fascinating and informative session:

- *'Extremely informative and geared towards cancer which increased its relevance. Helped to plug some of my knowledge gaps.'*
- *'Hugely interesting and useful to see where different organs are and how big they are and where they are in relation to each other.'*
- *'This was a fascinating session delivered in a brilliant way. Questions were answered well. Great interaction.'*

Students were able to learn about aspects of human anatomy which was relevant to themselves and their own cancer diagnosis:

- *'It was great to ask questions on the anatomy of the bowel.'*
- *'On a very personal level it was good to see actually the organs that have been affected by cancer in my own body.'*
- *'I think all patients should be given the opportunity to see such plasticised organs relevant to their treatment – if they choose to do so (i.e. not compulsory) – much more useful than a picture/diagram on a trial information sheet.'*

Several of the students commented on how seeing and touching the specimens was instrumental in helping them to understand how cancer can affect the body and was much more informative than simply looking at pictures:

- *'Infinitely better than trying to interpret scans, x-rays and 2 dimensional diagrams. My biggest surprise was the size and shape of the pancreas.'*
- *'[I now have] a better understanding of size and positioning of organs and why some are so difficult to get to and to treat.'*

The staff at the teaching centre were extremely welcoming and evidently very keen to talk to 'real' patients. Their manner was courteous and everyone was respectful of the donors:

- *'The staff and "students" were really excellent and were able to cope with any question we threw at them.'*
- *'It is always humbling to know that real people have donated their bodies to medical science and that these organs/bones etc. will help in the training of the next generation of doctors/consultants/surgeons.'*

A session on anatomy might seem misplaced in a workshop on research. So we asked the students how they thought this might help them with their understanding of clinical trials and got the following responses:

- *'Adds to the understanding needed to help design studies because knowledge of the anatomy can enable you to understand how parts of the body can be accessed/handled/treated etc.'*
- *'Superb support for understanding Clinical trials protocols - proximity of organs, better understanding of sites and how everything links.'*
- *'Being able to visualise the scale and treatment area or volume can help with understanding the limits that anatomy and physiology put on clinical trials so they don't adversely affect other body parts and organs.'*

The session was clearly a highlight of the course:

- *'How wonderful the human body is!!'*

Session 2: PROSPER – complex intervention

Since not all clinical trials are about testing drugs a session was included in the programme to teach the students about a non-drug trial – PROSPER. This is a trial looking at structured exercise programmes to prevent shoulder problems in women who undergo surgery for breast cancer.

Feedback from this session was positive:

- *'It was great to see a physio intervention – would be great to see something like this for bowel obstructions/adhesions.'*
- *'Physio treatment log/diary interesting to see.'*

Exercise as therapy was of particular interest to several of the students:

- *'An excellent example of a rigorous trial involving exercise that will hopefully show the real benefits to patients, rather than it being a "nice to have" recommendation and so hopefully will change clinical practice. A hobby-horse of mine is that exercise is an important part of any treatment and recovery.'*
- *'I see this type of trial more practical in the sense that it is hands on exercise. I feel exercise, if at all possible should be a must for anyone facing treatment.'*

As with some of the other sessions some felt that too little time had been allocated for this:

- *'Too little time but very interesting as was a different sort of study to the others we looked at.'*

This session also gave the students the opportunity to look around the Clinical Trials Unit (CTU) and talk to researchers who work with ICPV. Students also met some researchers who had minimal experience of working with patients as collaborators and were able to raise awareness of effective PPI.

Session 3: Mammo-50 & ICPV follow-up – mixed methods and patient led research – Janet Dunn, Sophie Gasson (SG)

ICPV had worked with Warwick CTU on the Mammo-50 trial from its very beginning. An ICPV member is a co-applicant of this study which is looking at the frequency of mammography for patients diagnosed and treated for early breast cancer. Janet talked through Mammo-50 as an example of a mixed methods study, explaining the qualitative sub-study and how this data is collected and analysed alongside the quantitative data. SG explained how focus groups and one-to-

one patient interviews had been conducted and were currently being analysed. There was discussion about the problems surrounding this and how they might be overcome.
Feedback from the session was positive and despite the sense that this was the end of the course and students were reaching saturation they reported some great learning:

- *'This worked really well as a practical session as it made me really think about the design of the trial and the different components that went into the trial.'*
- *'[I learned] how to gather patient experience in relation to survivorship.'*

Patient-led research was touched on was restricted by time constraints:

- *'A bit more discussion about Patient Led Research would have been useful. I'm thinking here were an individual has an idea for a research project, how do they go about getting funding, working with other researchers to support them.'*
- *'Standard practice across the UK is extremely variable. Patients can make a difference and instigate research for everyone's benefit.'*
- *'…patient led research should happen more often – not just for breast cancer patients.'*

Session 4: Practical – Dissemination of Results

Time constraints meant that this session did not go ahead as planned. Instead there was a brief discussion about the dissemination of results of clinical trials. JD was keen to get students thoughts on how results could be more effectively disseminated than they already are. Students appreciated the efforts of involving patients in this process and were keen to have more involvement:

- *Always good to be able to offer patient thoughts on this and other aspects of clinical trials.'*
- *'Getting research into practice is really important and I would like to know a bit more about this.'*
- *'Long term outcomes are particularly difficult to disseminate and new ways need to be found.'*

Take home messages from the course:

These were varied and plentiful! The students clearly learned a great deal and left the workshop wanting to know more. The following are some of the 'take home messages' the students left with:

- *'Trial design and analysis is complex but given good teaching, not difficult to understand!'*
- *'The results of any study are only an estimate and not a definite answer.'*
- *'Always good to dedicate time to study design – strengthens our ability to make meaningful input.'*
- *'Just how important it is to have a statistician involved in the early stages of designing a trial, and that one needs to be involved before the proposal is sent for funding.'*
- *'Just how important it is to make sure a patient is fully informed. It is vital to make sure the information is clear and explained fully.'*
- *'[There are] more opportunities to be involved in the design of studies than I realised. All CTU's should involve the public extensively with a mix of experienced and less experienced advocates. Want to work with CTU's now.'*
- *'PPI can contribute far more to the whole clinical trial and research process than it does at present (with notable exceptions).'*

The course was designed to help patients gain a better understanding of clinical trials and to enable them to be more effective patient advocates when working alongside researchers. We asked the students whether they would do anything extra or differently in terms of PPI as a result of attending this course. Answers were positive and diverse with many saying they felt more knowledgeable:

- 'I can understand studies much better which will help my various crusades with the NHS. I hope I can also use the scientific learning and that about research in survivorship.'
- 'My knowledge and understanding has been enhanced.'
- 'I will know what to look for when reviewing the results of any published trial.'

One with immediate effect:

- *'I think the course will help me when I give feedback on/write information sheets and consent forms for patients taking part in research projects. I have a couple of projects currently that I am involved with so the benefit for me is going to be immediate.'*

Some reported feeling more confident both in getting involved and in asking questions of the rest of a trial management team:

- *'I feel more confident about involvement in early stage trials.'*
- *'Keen to get involved more in study design in CTU's and to explore ways of getting more patients and carers involved.'*
- *'I should be able to ask questions more easily on the way trials are designed.'*
- *'Apply the learning I have gained and it has given me more confidence in being able to question things having gained more knowledge when doing so i.e. – not just asking totally naïve questions!'*
- *'I will question any PI who does not have a statistician involved in any trial proposal.'*
- *'I will think more strategically when helping to design a trial as part of the team.'*

General feedback from the students:

- *I have learnt so much!*
- *How much I still have to learn!*
- *I gained a better understanding of how to review research and what to look for.*
- *Great lecturer, passionate and enthusiastic about the subject. Made the sessions a real pleasure to attend.*
- *Great group, participation from everyone. Interesting discussions which everyone took part in.*

The pace of the course:

Quite a lot of the feedback suggested that parts of the course were too rushed or that more time could have been allocated to some of the sessions. A great deal of information was shared with the students, some of it new and some 'revision' and even with almost three full days it was difficult to deliver everything effectively. Asked about the pace of the course the students answered:

- *'Perfect although by about 5 I was a bit frazzled.'*
- *'Stats session went a bit too quickly at times!'*
- *'Too much information thrown at us in the lectures so hard to take it in. The practical sessions are very effective at applying the learning so more time on that would have helped. Still useful to have all the information handed out but perhaps don't try to deliver it all in lectures.'*

- *'We needed more time to cover the amount we did.'*
- *'I kept up, although I won't have remembered everything obviously. The notes we were given were good and so as/if I am asked to work on research projects I can refer to the notes for support.'*
- *'At times it was too rushed – a great deal was packed into each day – needed more time for reflection before moving onto next session at times.'*
- *'There was so much to cover in a relatively short space of time so that some "heavy" sessions will need to be re-visited in order to get a level of understanding (it takes some of us some time to understand complex concepts these days!)'*

Future Courses:

To help with planning further courses, we asked the students if there was anything else they would have liked to have learned about which wasn't on the programme. The following suggestions were made:

- 'I'm not sure how the Clinical Trials Units across the country work – together, independently? If researchers are in Cardiff, how do they get to work with the CTU in Warwick? How do ideas start and finish?'
- 'When Ethics Approval is needed/not needed in relation to trials, research?'
- 'More about stats and the nitty gritty (but I know this would take a long time!).'
- 'More examples of studies with some time devoted to each and … a wider range of cancers – very much breast dominated and ICPV now have members who have experience of a broad range of cancers.'
- 'I'm aware that sometimes things can go wrong and the protocol is breached. I don't really know what happens when this gets reported and what actions have to take place.'
- 'Perhaps in statistics, how the distribution models are chosen e.g. "t" distribution, $\chi 2$ distribution, "F" distribution etc. for particular data sets.'

There was a huge amount to pack into a sort space of time and this was reflected in the feedback about some of the sessions being too short to deliver effectively. Our take home message as organisers? The course should be repeated and offered to as many patient advocates as possible. The programme timings should be adjusted to enable each of the subjects to be taught more fully with consideration to possibly extending the course beyond three days:

- *There were of course a couple of occasions when we ran out of time to cover particular things, but I wouldn't want the course to be shortened by leaving material out. I would prefer the course to be made longer.*

Most Enjoyed?

The students clearly enjoyed the course and there was a great sense of camaraderie and shared learning throughout the three days. When asked for their 'most enjoyed' parts of the course these were some of the responses:

- *'I loved the enthusiasm of Janet Dunn and her colleagues which was just so infectious.'*
- *'Learning alongside a great group of people.'*
- *'The relaxed way in which the whole course was delivered.'*
- *'I enjoyed learning a great deal about statistics, the history of clinical trials and the design of trials.'*
- *'Everyone getting on with a common interest of PPI in cancer research, sharing common goals and common values.'*

And finally….

- *'Janet is an excellent teacher and it is very much appreciated that she spent her week with us.'*
- *'Wonderful to be part of an informative, inclusive experience and so many thanks to Janet and her team.'*
- *'It was of course an excellent course, with Janet's endless enthusiasm and knowledge, making light of some quite difficult ideas and concepts to comprehend, but I'm sure I'll need to revisit a lot of the slides in order for it to sink in (the older you get the longer it takes!)'*

Long awaited and anticipated, this workshop certainly delivered. ICPV would like to thank Janet and her team at the CTU for making this workshop possible. Also thanks to Hema Mistry and Julie Bruce for their teaching, Jamie Roebuck and the rest of the anatomy team at UHCW for making that session such a highlight and Nikki Morris for ferrying us between course locations by minibus. Thanks also to all the staff at Radcliffe who went out of their way to make us welcome.

Finally, thanks to Warwick CTU for their financial support, without which workshops like this would be impossible to run.

But most of all, huge thanks to Janet for her enthusiasm, support and exceptional teaching skills.