EXPLORING THE ROLE OF ADVOCATES IN

Breast Cancer Research

EUROPA DONNA
The European Breast Cancer Coalition

Introduction

EUROPA DONNA held a seminar on 14 June 2013 for its Executive Board members to define precisely the role of EUROPA DONNA advocates in breast cancer research. This is a complex area in which our Coalition has been involved and is increasingly being requested to participate. The European Commission requires member states to involve patients or lay persons in clinical trials and the assessment of clinical trial applications. As Europe's breast cancer advocacy organisation, EUROPA DONNA must have an informed, common voice. The Coalition needs advocates to represent it in breast cancer research initiatives. In order to represent women effectively, the advocates involved must understand the clinical trial or breast cancer research process and the role of clinical trial committees. They must also have the time and resources to enable them to participate.

The seminar aimed to elucidate the specific areas in which advocates can and should make contributions to clinical trials and research, and to outline the type of training the Coalition should provide so that its advocates can evaluate trials and provide meaningful input into committee meetings and/or documents related to research. It was suggested that Fora should identify an advocate with an interest in research and good English skills to become the scientific leader of their group. Among EUROPA DONNA advocates, there are many scientists, doctors, health care workers and women interested in research. Close working relationships with scientists should also be nurtured.

At the seminar, Olivia Pagani, a clinical oncologist with much clinical trial experience, was the scientific leader. She gave an overview of the clinical trial process and issues of relevance to advocates and answered questions throughout. EUROPA DONNA Executive Director Susan Knox then described EUROPA DONNA's past and ongoing role in the MINDACT trial run by Breast International Group (BIG), a non-profit network of global research groups. Maggie Wilcox, a former nurse, breast cancer survivor and board member of the UK organisation Independent Cancer Patients' Voice (ICPV), gave a hands-on account of how her organisation, which provides the patient perspective for many research initiatives, has a strong voice which is sought and listened to in the UK.

The presentations addressed a number of questions raised regarding the conduct of clinical trials and are summarised in the highlights of the presentations and discussions in this booklet. Some of the questions raised regarding the role of the advocates in breast cancer research and next steps to further EUROPA DONNA advocacy involvement in research are provided at the end of the document.

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Highlights: How clinical trials work and what role advocates can play from the scientists' perspective

Presented by Olivia Pagani, Staff Oncologist, Institute of Southern Switzerland

Clinical trials are becoming increasingly more complex and it is essential for breast cancer advocates to understand them and, where appropriate, to play a role from the very preliminary stages of a trial. There are different types of studies and trial phases that may benefit from the input of advocates.

Types of clinical trials and their aims

Drug development trials

Aim: To test "new" drugs after preclinical research. These include phase I (first in human), phase II, and phase III (registration) trials
e.g., everolimus, eribulin, etc.

New indications

Aim: To test new indications for "old" drugs
e.g., tamoxifen for primary prevention

Combination trials

Aim: To test new combinations or sequences for "old" drugs
e.g., lapatinib + trastuzumab

Trials of surgical techniques or non-pharmacological approaches

Aim: To test new therapeutic approaches/techniques
e.g., partial breast irradiation with no axillary dissection with positive sentinel node biopsy

Breast cancer trials have a number of aims (i.e., what the trial is testing the ability to achieve):

- Prevention of breast cancer
- Prevention of invasive breast cancer in women with intraepithelial neoplasia (non-invasive forms such as ductal carcinoma in situ, lobular carcinoma in situ)
- Prevention of relapse (adjuvant setting)
- Prevention of progression (advanced disease)

Note: Detailed information on trials and breast cancer research is available in EUROPA DONNA's booklets *Clinical Trials and Breast Cancer* and *The Advocate's Guide to Understanding Breast Cancer Research* (available on www.europadonna.org)

Potential role of advocates in drug development trials

Phase I trials can be the first time a drug is administered in humans to determine its safety and toxicity. From a patient's perspective, it is the most demanding trial phase, due to close monitoring and multiple visits with doctors. Given the nature of these trials, informed consent must be carefully constructed and communicated to the participants, who must clearly understand their chance of having no treatment benefit from the drug being tested.

Possible advocate role → Input into informed consent documents and ensuring women understand the potential risks and benefits of participating in a phase I trial.

Phase III trials – the final phase required for registration of a drug – have an important potential role for advocates. They involve a large number of participants and high investment.

Possible advocate role → Input from the very beginning, into the design of the protocol for the trial, the informed consent, potential inclusion on the Independent Data Monitoring Committee (IDMC).

Long-term toxicity studies and post-marketing studies could be a key area for involvement of advocates. Monitoring of long-term toxicity is often not included in the regulatory requirements for the marketing of a drug. This may provide challenges for funding. Patients need to be followed up and contacted.

Possible advocate role → Ensure such follow-up studies are being performed; encourage women to report adverse events, recurrences, etc.; demand quality controlled data surveillance and cancer registries.

Trials testing non-pharmacological interventions are ideal for advocate involvement since they are not pharmaceutical industry trials. However, funding may therefore be an issue. Epidemiological studies, lifestyle-related prevention trials and outcomes of pregnancy after breast cancer are a few examples.

Possible advocate role → Encourage the performance of such trials and inform women how they can participate (e.g., in prospective or retrospective trials).

The Independent Data Monitoring Committee

Patient representatives can be involved in the IDMC – also known as the Data and Safety Monitoring Board, an independent committee responsible for verifying all ongoing trial data to ensure the safety of the participants. All data, including toxicity data are measured every 6 months, and are unblinded (i.e., the IDMC knows which patients are receiving which treatment). Reports issued by the IDMC can stop a trial or change the protocol. For example, in the ALTTO trial, women receiving the study drug alone (lapatinib) discontinued treatment since the drug alone was unlikely to meet the prespecified criteria to demonstrate non-inferiority to trastuzumab alone with respect to disease-free survival.

Academic and government versus industry-run trials

The cost of cancer research and trials has grown exponentially in recent years (an estimated 55% from the period 1995-2000 to 2000-2002). The majority of drug trials are sponsored by the pharmaceutical industry. Some trials such as those in the BIG or the International Breast Cancer Study Group are run by academic centres. The difference between the two lies in the "owning" of the data. While a drug company may provide funding and supply the trial medication, the academic centre in charge owns and is responsible for the data collected.

Some government-led and sponsored trials are being performed, such as a Finnish trial examining a shorter administration of trastuzumab (9 weeks rather than the standard 1 year of treatment).

Possible advocate role → Be aware of trials being performed in your own countries, by academic centres and government. Encourage involvement in larger consortia. While advocate involvement in industry-run trials may compromise the division between advocates and industry, advocate involvement may be important. Any involvement should begin at the very conception of a trial, rather than having advocates called in to save face if issues arise during the conduct of the trial.

Importance of collaboration

Trial consortia and collaborative groups enable the performance of trials that otherwise would be difficult or impossible for individual centres to activate on their own. Trials must have strong scientific committees to defend the role of the academics and their possession of the data against the drug companies. Global collaboration also helps to avoid duplication or repetition of trials.

As many clinical trials are now being run in countries such as India and China, it is important to encourage research centres in these countries to belong to international consortia. This would help to ensure standards for trial results and for women participating in trials in those countries.

Possible advocate role → Check that trials in their countries are being conducted according to the currently approved protocol/amendments, good clinical practice and all regulatory requirements. Encourage involvement in trial networks. Check the investigators' qualifications, resources and compliance to the protocol and regulatory requirements. Ensure that the trial data are accurate, complete and verifiable from source documents.

Additional crucial aspects to clinical research

To ensure that trials provide reliable results that are useful for women they need to address relevant and interesting questions. Besides effectiveness of a drug or intervention, they should assess effects on women's quality of life and should be reproducible in the real world. Selection bias, whereby trial participants do not necessarily reflect the actual population or do not effectively reflect racial minorities or certain age groups, also needs to be avoided. Direct head-to-head studies of similar treatments are of little interest to advocates.

Possible advocate role → Ensure that a trial addresses questions of interest and use to women and that they are representative of all women in the population. See that a useful drug or technique is available in all countries. In the health technology assessments, defend the need for effective drugs to be made available.

Possible roles for advocates in clinical trials

- To understand the clinical trial process and remain abreast of scientific research
- To promote relevant clinical trials that address important questions
- To be involved from the very beginning of a trial (from the design of the protocol) and provide input on patient documents such as the Informed Consent
- To encourage non-pharmacological trials (e.g., quality of life studies, etc.)
- To support investigators' needs in terms of independent clinical research
- To consider participation in IDMCs
- To control for accuracy and good practice of trial conduct (e.g., through ethics committees)
- To advocate for dissemination of study results and availability of effective drugs across all countries

PRACTICAL APPLICATIONS

Highlights: EUROPA DONNA's role in the MINDACT trial and European breast cancer research

Presented by Susan Knox, EUROPA DONNA Executive Director

The demand for EUROPA DONNA's input into breast cancer studies has grown since the Coalition joined its first trial in 2005. Our involvement in the MINDACT (microarray for node negative disease may avoid chemotherapy) study arose due to our involvement in the international TRANSBIG research network. The trial was of interest to advocates as it set out to determine if a group of patients could be spared chemotherapy and was being performed by reputable scientific bodies (BIG and EORTC). EUROPA DONNA has been involved in this ongoing trial since the beginning as part of the Steering Committee, Legal/Ethics Committee and the Spreading of Excellence Committee. Our responsibility has been to provide input from a patient's perspective and to help communicate information about the trial to the public.

Different committees and our function

Steering Committee

One EUROPA DONNA member participates in this committee of 43 members, including all the institutions involved, clinicians and researchers. Involvement has included working on all aspects of trial design and reviewing all documents, meeting twice a year and participating in teleconferences. Members must stay up to date and be prepared before attending meetings and reviewing minutes. Membership in the consortium has changed over the duration of the trial.

Legal and Ethics Committee

EUROPA DONNA members served on this committee to review consent agreements and patient information sheets and to resolve the ethical issues that have been raised. The MINDACT trial involves transporting biological materials from participating countries to the Netherlands for analysis, and the ensuing ethical and legal issues with the transfer of biological materials across borders. The function has also been to see that the trial is conducted in accordance with all laws and international treaties and accepted ethical standards. It also involved reviewing and approving the patient consent forms.

Spreading of Excellence Committee

Although this committee no longer exists, a EUROPA DONNA member took part in meetings twice a year and teleconferences in order to review, develop, and disseminate information, documents and educational materials on the project. EUROPA DONNA was instrumental in developing a DVD that explained the purpose of the trial for patients to watch with their nurse or doctor. Research is needed to see if this DVD approach was effective.

What we have learned from the MINDACT experience

- EUROPA DONNA members participating on the committees need to be prepared and able to review extensive documents
- Trial protocols can change part way into a trial
- The advocate's role is important in ensuring the readability of all the materials that are given to women and to see that women are given a balanced view and are informed of trials that are ongoing

Current situation

EUROPA DONNA receives numerous requests to participate in European research including F7 projects of the European Commission. EUROPA DONNA has representation on the BIG Scientific Committee, as well as various BIG-related studies, including the American Breast Cancer Group (NABCG) working group on survivorship, and the AURORA study. It is essential that we be able to analyse scientific documents, respond on a timely basis, and participate in all research projects relevant to breast cancer.

When evaluating participation in a research project advocates should:

1. Proceed carefully and thoughtfully from the outset; consider who is conducting the trial; what is the important question the trial will answer for patients
2. Start with one trial only that complements your goals
3. Ensure adequate resources; identify trained advocates available with time to dedicate to the project
4. Understand time commitment: meetings, teleconferences, review materials, lengthy, complex documents
5. Obtain funding for advocacy work, i.e., administration, time, resources, etc. from trial group in advance
6. Study application; understand what roles you are prepared to play and which you are not and state this clearly
7. Be attentive – advocates are not there to rubber stamp the materials
8. Be assertive when necessary; advocates need time to study materials in advance, ask questions and participate actively in order to ensure credibility, independence, and provide a real consumer perspective

EUROPA DONNA is in a unique position, as a coalition of 46 member countries, to be able to provide input into trials from a patient's perspective, to see that patients' needs are being addressed, and to communicate key information effectively to potential and actual trial participants. Our advocates have a wide range of relevant backgrounds to be able to do this, from law, to science, to research and, above all, to being patients themselves.

Highlights: How advocates can contribute to research – Independent Cancer Patients' Voice

Presented by Maggie Wilcox, President of Independent Cancer Patients' Voice, United Kingdom

Independent Cancer Patients' Voice (ICPV; www.independentcancerpatientsvoice.org.uk) is a charity founded in the United Kingdom in 2009 that works to involve patients with clinical research (including clinical trials, working with clinical/academic units, tissue banks, etc.). ICPV is a patient advocate group run and led by patients, whose aim is to bring the patients' voice to the cancer research community. While the group's focus is on cancer in general, it was founded by a group of breast cancer patients with an interest in research, and many of its activities involve breast cancer.

Three members were involved in the National Cancer Research Institute's Breast Clinical Study Group (BCSG). General initial reactions to the involvement of patients on research committees were not always favourable, but with the passage of time opponents began to request their input. When the lay members designed a questionnaire to gauge the value of their contribution to the BCSG as viewed by professional colleagues, more than 95% of respondents believed there is scope for consumer members to attend additional meetings which are important to the role and function of clinical study groups (e.g., subgroup meetings, annual trials day, National Institute for Clinical Excellence [NICE] meetings). Since then, ICPV has gained influence and led to changes in approaches to research. They have rewritten patient information leaflets, influenced trial design to make it more likely for patients to enrol and encouraged patients to join trials by sharing their own experiences.

ICPC members are involved in the design and running of a number of clinical studies, helping to ensure that they are targeted effectively. They contribute at a strategic level with clinicians and clinical researchers and have different levels of involvement. In some studies, they contribute to the development of funding proposals, read and comment on trial protocols and on patient information materials. Members sit on the steering committees to ensure that the patient's perspective is considered.

In addition to trials, they have been instrumental in working with the Breast Cancer Campaign's Tissue Bank. Two advocates were involved from the inception and participated in tissue bank site visits and inspection. They suggested that groups collecting tissue should work together, which led to the formation of a larger tissue bank, as well as to changes to the tissue access policy. Now no tissue is released from the tissue bank without a lay person's approval of the lay summary written by the researchers. The group also created a leaflet for patients featuring patient testimonials that encourage tissue donation.

Examples of other main activities

ICPV Study Days

The group organises study days in different locations throughout the UK on different topics of current relevance to research. They aim to encourage debate with clinicians and researchers on an equal footing. Many of these days are hosted by academic centres, such as universities. This provides the advocates with easy access to professionals for teaching and debate and a venue free of charge, while also giving a wide geographical spread across the country. They have found that work at a local level contributes information for their work at a national level. Some of the topics of the Study Days include pathology and tissue banking; trial design, multidisciplinary team meetings for metastatic disease and genetics; statistics, ethics and surgical trials; radiotherapy, and more. In addition to informing advocates and ensuring that they can make a valuable difference to user involvement in research, this has helped the group to build excellent relationships with the research community.

Dragon's Den

Using the format of the Dragon's Den television programme, where entrepreneurs pitch their ideas to potential investors, IPCV holds a similar debate for researchers to give a 15-minute presentation on proposed studies that may have patient barriers. It creates a forum for debate and patient representatives provide their feedback. Each study now has ICPV member in the working group.

Recommendations for increasing advocate participation in research

- Foster relationships with specific researchers who will encourage patient advocate involvement, such as finding one key scientist to promote involvement
- Find collaborating partners (or leverage current relationships with collaborating organisations)
- Promote attendance of advocates at breast cancer conferences
- Do not get discouraged by possible lack of enthusiasm about patient involvement by some researchers: many change their minds and are pleased to have us involved

Notes

Questions for advocates to answer when considering a role or already engaged in a clinical trial

1. Trial design: does the purpose fit goals/ethics of EUROPA DONNA? Is the question being studied important for patients and will it benefit them?
2. What organisation is carrying out the trial? Is this a consortium/academic group whose work in breast cancer is well established?
3. Ethical considerations. Are there any issues that need to be resolved? This may include information for patients, the full disclosure of trial results; what treatment patients will receive if a trial is stopped; what is the treatment if the drug not available in the participant's country; is tissue saved for use or study at a later time, and under what conditions? Will information be disclosed that could impact the patient negatively in the future i.e., insurance, employment, etc.?
4. Is the language used, especially in consent forms, understandable and user friendly?
5. Are all aspects of the trial transparent or are parts of the trial or trial design kept confidential?
6. Does the trial involve a pharmaceutical company? What is its role? How involved is it in the running of the trial? Could it be a compromising situation for advocates?
7. How will the trial committee handle requests/recommendations provided by patient advocate members?

Recommendations for advocates who become involved in the breast cancer research process

- *Ensure that any involvement in a clinical trial committee occurs from the outset of a trial*
- *See that a trial addresses questions of interest and use to women*
- *Be prepared to provide input on clinical trial protocols, design, patient information documents and consent forms*
- *Get involved in epidemiological studies (e.g., lifestyle-related studies) that are not testing a certain product/treatment*
- *Ensure that post-marketing/long-term toxicity studies are being performed*
- *Encourage local or national research initiatives to become part of larger research consortia or clinical trial networks and ensure that they meet the requirements for good clinical practice*
- *Participate in academic-run trials rather than industry-run trials*
- *Encourage women to consider participating in trials generally but without recommending specific trials. (e.g., by providing information, answering questions, addressing concerns)*
- *Use the EUROPA DONNA booklets* Clinical Trials and Breast Cancer *and* The Advocate's Guide to Understanding Breast Cancer Research *and the ED website as background*

Next steps for EUROPA DONNA to engage its advocates in the breast cancer research process

- Ensure that EUROPA DONNA board members become involved in some area of the Coalition's research activity
- Include a research training module for interested advocates as part of the next EUROPA DONNA Advocacy Leader Conference and possibly the next Pan-European Conference (2015)
- Ask EUROPA DONNA Fora to recommend an advocate with knowledge of or an interest in breast cancer research, a good level of English and time available to take part in the next training sessions and then to participate in research at a national level
- Use EUROPA DONNA's current collaborations and contacts with research groups, their professional members and resources (e.g., websites, conferences) to keep advocates up to date on current key topics in research
- Find "clinical champions/advisors", a researcher or physician, at a European level or at national levels to promote the inclusion of advocates on clinical trial committees and to provide guidance to them during their involvement
- Hold research training workshops for advocates involved in research on a regular basis. Encourage advocates who choose to be involved in the "research group" to attend main scientific conferences, as a representative of their organisation (e.g., if a Forum plans to send an advocate to EBCC consider sending their "research advocate")

Notes

EUROPA DONNA – The European Breast Cancer Coalition Trial/ Research Evaluation Criteria

Because controlled clinical trials are the safest way to evaluate new treatments and procedures for breast cancer, EUROPA DONNA promotes awareness about clinical trials and works with research organisations to improve trial design and monitoring, educate the medical community and consumers, and promote initiation of high quality breast cancer trials. Before forming a partnership with any institution or consortium to participate in one or more clinical trials, EUROPA DONNA carefully evaluates the proposed clinical trials based on these principles:

1. The study must be designed to answer an important, novel question relevant to breast cancer.
2. The study must be a well-designed clinical trial. It must be scientifically rigorous, and employ appropriate and meaningful outcomes.
3. The study must be conducted in an ethical manner. There must be sufficient data supporting efficacy and safety. Participants must have sufficient information to provide meaningful informed consent, and the study must be approved by an Ethics Committee (EC) or Institutional Review Board (IRB). The trial must employ mechanisms to provide adequate protection for participant privacy and the confidentiality of participant information. There must be a system in place such as a data and safety monitoring committee for evaluating the protocol and patient safety as the trial proceeds.
4. The research team conducting the trial must follow the guidelines established by the World Medical Association Declaration of Helsinki in the document subtitled, "Ethical Principles for Medical Research Involving Human Subjects."
5. The trial must adhere to European Parliament legislation requiring adherence to the Good Clinical Practice Guidelines and the Clinical Trial Directive.

The trial must meet EUROPA DONNA's expectations, which are listed below.

In a partnership between EUROPA DONNA and a research organisation EUROPA DONNA will contribute the following:

- EUROPA DONNA will provide formal and informal input from knowledgeable patient advocates on study design and implementation. ED will be invited to participate from the outset.
- EUROPA DONNA will assist in disseminating information concerning the trial to the lay public and advocates through its network, its conferences, and its advocacy training course.
- EUROPA DONNA will not participate in accrual, but will assist in making trial information accessible to the public.

EUROPA DONNA expects the research organisation to provide the following:

- The research institution will provide ED with a copy of the draft protocol and accompanying literature, the informed consent document, full disclosure from study authors, and full disclosure on sponsorship.
- The research institution will afford EUROPA DONNA opportunities for meaningful input into study design and implementation. For example, EUROPA DONNA representatives may sit on study committees and data and safety monitoring committees.

- The organisers will provide EUROPA DONNA with opportunities for meaningful review of and input regarding safety data.
- The trial organiser will provide EUROPA DONNA with information about every breast cancer clinical trial they are conducting.
- To the extent feasible the organiser will provide trial participants and breast cancer advocates including ED with updates on the trial's progress, status and results, even if the trial is cancelled or ends early.
- The primary results of the study will be published in full form in a respected peer-reviewed journal. The findings will be disseminated regardless of final EMA approval, the strength or direction of the results, or findings of significant adverse events.

Should the research organisation request input or advice from ED concerning a trial already in progress, ED will decide on an ad hoc basis whether or not this is appropriate/advisable from our perspective. In order to consider this, ED must be provided with copy of trial protocol and accompanying literature, the informed consent document, full disclosure from study authors, full disclosure on sponsorship, and any results already obtained. If the study does not meet the criteria listed above, ED will decline giving its input or advice.

Considering a possible collaboration with any entity, public or private, or any consortium public or private does not constitute agreement on the part of EUROPA DONNA to lend its name, logo, image, or resources to the endeavour. In all cases ED must give specific written approval for its name and logo to be used in connection with any research activity.

A committee consisting of ED Executive Director and 3 members of the Board will be consulted concerning decisions on ED's participation in clinical research of any kind.

Notes

Mission

EUROPA DONNA – The European Breast Cancer Coalition is an independent, non-profit organisation whose members are affiliated groups from throughout Europe. The Coalition works to raise awareness of breast cancer and to mobilise the support of European women in pressing for improved breast cancer education, appropriate screening, optimal treatment and care and increased funding for research. EUROPA DONNA represents the interests of European women regarding breast cancer to local and national authorities as well as to institutions of the European Union.

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