CLINICAL RESEARCH MATTERS TO YOU:
DO YOU WANT TO KNOW MORE? THE FILM'S STORY

WHY PRODUCING A FILM?

In most European countries clinical trials are rarely the subject of debate among citizen or consumers or patients organizations, in fact there has not been a strategy on how to communicate the importance of independent multinational clinical trials. Still more rarely are the research priorities discussed a priori in an open debate between researchers, clinicians, and patients. The involvement of European citizens in supporting independent clinical trials, as a method to lead health care assistance decisions, varies among countries. Studies have shown that misconceptions about clinical trials are frequent, and that the level of participation in clinical trials is low. For these reasons, it is important to empower citizens and health consumers on the crucial aspects of clinical research, and increase their awareness of independent clinical trials.

Short films are available on the web (youtube or similar), mostly related to personal experience or particular health conditions, generic, and not planned to offer a general overview of the method supporting a high quality clinical trial. This panorama is supported also by the resources collection of communicating information about clinical trials in Europe, done in the framework of the activities of one of the work package of the project.

The film is an efficient tool of mass communication, considering its wide possibilities of use: television, internet, social networks, *ad hoc* display, or *ad hoc* plain language package. As reported in the Health Communicator's Social Media Toolkit the film/video has a high impact in term of dissemination, and can be a great way to exchange information.

KEY WORDS AND EXPERTIES

The film has been structured as an animated story covering the ECRAN key words:

- *uncertainty:* the principle of a clinical trial, when it is genuinely unsure which treatment is best for a patient,
- *control-comparison:* the treatment proposed in a clinical trial has to be compared with the best possible evidence-based alternative,
- *randomisation:* deliberate element of chance for the assignment of treatments,
- *outcomes:* outcomes provide evidence about benefits and risks, therefore outcomes must have outstanding clinical significance and so must matter to patients,
- *independent clinical research*,
- *need for multinational clinical trials:* to promote coordinate activities among European clinical research centre.

These key words were discussed and agreed among the ECRAN partners of the project accordingly with the main messages of the project:

- the importance of public understanding of the need for and basic principles of clinical trials, thus fostering active involvement of patients in trials and of their representatives in trial design,
- the need for independent clinical trials driven by healthcare issues, to optimise treatment strategies through comparison of benefits and harms of multiple therapeutic (drug and non-drug) options, thus supporting evidence-based clinical practice and reduction in healthcare inequalities,
- the need for transparency and optimal use of data, to promote the cost-effectiveness of treatments and to reduce the economic burden of diseases,

- the need for multinational cooperation, taking advantage of European population size and diversity, and of its medical expertise.

The production of the film, in the framework of the ECRAN project, is the result of a co-operation between the consortium members, Mario Negri Institute, the RAI-science magazine Super Quark (RAI is the principal public Italian television channel, and Quark is a science column designed and conducted by Piero Angela, broadcast from March 1981), and Bozzetto Studio (http://studiobozzetto.com/). In particular:

- methodologists directly involved in clinical trials and coordinators of network of researchers and clinicians, such as INSERM and the Mario Negri Institute,
- methodologists involved in the evaluation of clinical research, such as Oxford University, Copenhagen University Hospital Copenhagen Trial Unit, University of Freiburg, German Network of clinical research centres,
- researchers involved in partnership collaboration with citizens and patients, Cochrane Consumer Network (responsible for supporting consumers and promoting consumer involvement in health debate), European AIDS Treatment Group (a European network of nationally-based volunteer activists affected by HIV/AIDS from 40 countries in Europe), and Mario Negri Institute (a non profit organization with an ad hoc research laboratory on consumers involvement in health setting),
- experts of science communication, as Zadig and RAI-SuperQuark.

FROM THE IDEA TO THE STORY BOARD

The film starts from the James Lind story: the naval surgeon James Lind in 1747 showed that the two sailors treated with oranges and a lemon were cured of scurvy while the other 10 sailors, treated with other remedies, remained ill. Afterwards each module of the film covers a specific topic through animated sketches and video. The role of the European Commission to support independent multinational clinical trials has been covered in the film to stress the importance of healthcare-oriented clinical research.

The first draft (Annex 1) was discussed with SuperQuark staff in terms of feasibility and practicability during several face-to-face meetings. On the basis of all the comments and suggestions of the ECRAN partners the draft was reviewed and presented and discussed with Bozzetto &CO studio. All aspects of the film were thoroughly discussed and a first version of the story board was finalised. Considering the target of the ECRAN Project - primarily patients and citizens, and their representatives - the story board reflects the plan to have a simple and direct representation of the keywords to be covered by the film. The characters are male and female without particular characteristics so as to be recognised by a large group of European citizens. To catch the attention of the public an ironic and humorous style has been chosen to describe situations and figures. The sound of the ECRAN film is evocative of the different situations presented in the film.

The first story board was discussed with ECRAN partners where two groups representing European patients and citizens are present, EATG and CCNET group, respectively.

Also the External Advisory Board of the ECRAN project saw and appreciated the first draft of the animated film. As a result of comments and suggestions, seven versions of the story board have been produced, each version accompanied by an hoc text or notes explaining changes and differences. The first page of the last and final version is presented in Annex 2.

THE DUBBING PROCESS

The dubbing process is a multifactor process since voice, imagines and sounds must be synchronised according to the original film. Moreover it is important to preserve the original spirit of the film in each language. For these reasons, the different texts has not simply been translated, but also revised by experts and the Studio Bozzetto has continuously contacted the coordinator of the film during the dubbing process making changes and adjustments in order to obtain the best result for each language. ECRAN film is dubbed in 23 different languages covering a total of 28 countries.

EU OFFICIAL LANGUAGES	COUNTRIES
01. Bulgarian	Bulgaria
02. Czech	Czech Republic, Slovakia
03. Danish	Denmark, Germany
04. Dutch	Netherlands, Belgium
05. English	United Kingdom, Ireland, Malta
06. Estonian	Estonia
07. Finnish	Finland
08. French	France, Belgium, Luxembourg, Italy
09. German	Germany, Austria, Luxembourg, Italy, Belgium
10. Greek	Greece, Cyprus
11. Hungarian	Hungary, Austria, Romania, Slovenia, Slovakia
12. Irish	Ireland, United Kingdom
13. Italian	Italy, Slovenia
14. Latvian	Latvia
15. Lithuanian	Lithuania
16. Maltese	Malta
17. Polish	Poland
18. Portuguese	Portugal
19. Romanian	Romania
20. Slovak	Slovakia, Czech Republic
21. Slovene	Slovenia, Austria, Italy, Hungary
22. Spanish	Spain
23. Swedish	Sweden, Finland

The dubbing process started by translating the original Italian manuscript in English. The English version of the ECRAN film is very important because the English speaking community is very large, but also because many non-native English consumers/people/citizens will view the English version of the film. In fact, English is the most fluently spoken foreign language among European citizens (32%) (6). After the first translation of the original Italian manuscript (presented and distributed during ECRAN January 2013 meeting), the English manuscript has been revised by a native English speaker of the Mario Negri Editing Office. This manuscript has been then reviewed by the ECRAN English partners (Oxford University Hospital & Cochrane Collaboration-CCNet) and, after several discussion and changes we agreed on the version reported in the Annex 2. At the end of this process the English version could be considered clear and fluent both for the English native and for the non-native English

audience. This manuscript is the pivotal text for all translations in 23 EU languages. The following points, considered and discussed during each translation and review process by the experts, are important for manuscripts translations as close as possible to the original version:

- in the framework of the ECRAN project, the animated film is a tool, is not a compendium on the methods of clinical research. Obviously, the animated film presents some simplifications. The film is intended as a tool for conveying basic information while stimulating curiosity for clinical research and encouraging a deeper look to the other tools developed within the project (that will be available on the ECRAN website);
- voice, pictures and sounds must be synchronized in all the 23 EU languages, for this reason it is important to follow as much as possible the Italian or English version,
- it is very important that the translation does not change the spirit and the user-friendliness of the message of the ECRAN film,
- for technical reasons - and costs - it was not possible to modify the original story board of the film according with each language.

The flow chart of the translation process is presented in the scheme below.

REFERENCE TEXT

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TRANSLATION OF THE TEXT IN ONE OF THE 23 EU LANGUAGES MADE BY A NATIVE PROFESSIONAL TRANSLATOR, NOT NECESSARILY EXPERT IN CLINICAL TRIAL FIELD

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FOR EACH OF THE 23 EU LANGUAGES THE TRANSLATED TEXT HAS BEEN REVIEWED BY AN EXPERT OF CLINICAL TRIAL METHODOLOGY

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PRODUCTION OF THE FINAL TEXT FOR EACH OF THE 23 EU LANGUAGES

According to the experience and the expertise of the Studio Bozzetto&co., there were two possibilities for the different languages. For some languages a single voice was proposed, as already tested. For other languages different voices were proposed.

- First possibility: one voice already tested and used for other films and considered standard voice. For this voice - Dutch, English, French, German, Italian, Portuguese, Romanian and Spain – the local review listened and approved the voice.
- Second possibility: different voices to be listened and chosen to be adequate to the film. This is the case of Bulgarian, Czech, Danish, Estonian, Finnish, Greek, Hungarian, Irish, Hungarian, Irish, Latvian, Lithuanian, Maltese, Polish, Slovak, Slovene, and Swedish - the local review listened and chose the voice. A list of 57 different voices were considered.

COLLABORATION

Some partners of the ECRAN project are also involved in the *European Clinical Research Infrastructures Network* (*ECRIN*) a no-profit infrastructure which supports multinational clinical research projects in Europe (http://www.ecrin.org). Through this network some ECRIN clinical researchers were asked to review the text of the film translated in their native language. Moreover, through the collaborative network of the WP leader, other collaborations have been request to review the texts of the film. Finally, all the ECRAN partners have been involved for their country of origin.

ECRAN Partners	
Antes Gerd	University Medical Center Freiburg, Universitätsklinikum Germany
Burls Amanda, Chalmers Iain	Oxford University Hospitals, United Kingdom
Dedes Nikos	European AIDS Treatment Group
Demotes Jacques	Institute National de la Santé e de la Recherche Médicale, France
Gluud Christian	Rigshospitalet, Copenhagen University Hospital Copenhagen Trial Unit, Denmark
Gyte Gill, McIlwain Catherine	Cochrane Consumer Network
Wolf Stefanie, Post Nils	Network of the Coordinating Centres for Clinical Trials, Germany
EUROPEAN RESEARCHERS INVOLVED THROUGH THE ECRIN NETWORK	
Blaskó Gyorgy	University of Szeged Albert Szent Györgyi Clinical Centre Clinical Research Coordination Centre Szeged, Hungary
Brabencová Marianna	Department of Pharmacology, Faculty of Medicine, Masaryk University Kamenice, Czesh Republic
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Callus Edward	Pediatric & Adult Congenital Heart Disease Centre, IRCCS Policlinico San Donato, Italy
de Winter Ron	Julius Center for Health Sciences and Primary Care, Biostatistics & Research Support, Utrecht, The Netherlands
Demlova Regina	Department of Pharmacology, Faculty of Medicine, Masaryk University Kamenice, Czesh Republic
Gaynor Siobhan	Molecular Medicine Institute, Ireland
Lennon Susan	Molecular Medicine Institute, Ireland
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Szmigielski Cesary	Medical University of Warsaw, Poland
Szofer-Araya Alicja	ECRIN - European Clinical Research Infrastructures Network INSERM - Institut de Santé Publique, France
Pehrman Heli	FinnMedi Oy, Tampere, Finland
Sandra Chesley, Pierre Lafolie	Molecular Biology Scientific Officer Drug Safety and Evaluation Sector, Department of Clinical Pharmacology, Karolinska University Hospital Solna, Sweden
EUROPEAN RESEARCHERS INVOLVED THROUGH THE MARIO NEGRI NETWORK	
Beeg Marten	Department of Molecular Biochemistry and Pharmacology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Italy
Bonovas Stefanos	Department of Pharmacology, School of Medicine, University of Athens, Athens, Greece
Chripkova Martina	Department of Oncology, IRCCS-Istituto Mario Negri, Milano
Drutovic David	Department of Oncology, IRCCS-Istituto Mario Negri, Milano
Ene-Iordache Bogdan.	Department Biomedical Engineering, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Italy
Gonzalez Lorenzo Marien	Clinical Epidemiology Unit, IRCCS Galeazzi Orthopedic Institute Department of Biomedical Sciences for Health, University of Milan
Petrov Ilian	Department of Drug Development, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Italy
Pliuškys Laurynas	The Botnar Research Centre Institute of Musculoskeletal Sciences, University of Oxford
Poikane Sandra	EC Joint Research Centre, Institute for Environment and Sustainability-Ispra, Italy
Zupan Jerica	MBA European Commission DG Joint Research Centre, Institute for Health and Consumer Protection Task Force on Public Health-Cancer Policy Support-Ispra, Italy

The **ECRAN film** owns to the ECRAN-IRCCS Institute Mario Negri, as coordinator of the project. The film is not issued for commercial use or commercial distribution, and it is intended as a tool for the ECRAN project dissemination:

- free download under a creative commons licence in 23 European languages, www.ECRANproject.eu
- its modular structure allows to display the whole film or its 8 different modules about: A clinical trial, Ethics committees, Randomization, Double blinding, Analysing the data, One trial is not enough..., Outcomes have to be important to patients, Some pitfalls of trials.

ANNEX 1

In 1747, a Scottish naval surgeon – James Lind - was uncertain how to treat the scurvy that was killing his sailor patients. The august Royal College of Physicians recommended sulphuric acid; the Admiralty favoured vinegar; others thought that sea water or cider were what was needed; still others thought the answer lay in potions using herbs; and some experienced mariners had thought for many years that citrus fruits prevented and cured the disease. Faced with these conflicting opinions, James Lind organised a controlled trial in which 12 sailors at similar stages of the disease who were eating the same basic diet and being cared for in the same part of the ship were divided into 6 pairs of sailors, each pair then being given one of the six treatments. Each of the pair who received two oranges and a lemon recovered rapidly, whereas the other ten sailors remained unwell. Lind's comparative test dealt with his uncertainty and revealed the most effective treatments.
[http://www.jameslindlibrary.org/illustrating/records/a-treatise-of-the-scurvy-in-three-parts-containing-an-inquiry/other_materials]

Medical care has changed a lot since the 18th century, but the logic of comparative trials to address uncertainties about the relative merits and disadvantages of alternative treatments remains just as important today as it did then.

Before a treatment can be adopted with confidence, evidence is required to show that it is more likely to do good than harm. For some drugs this may start with the design of potentially effective molecules tested on cells and animals in laboratories before being tested in healthy volunteers, to assess the doses that human beings can tolerate.

The ultimate tests of whether treatments – whether they are drugs or one of the many other non-drug forms of treatment - are worthwhile are done in patients with particular diseases and health problems.

These late phase clinical trials, involving well informed patients, are thus done to address these remaining uncertainties about the effects of treatments, and to assess the effects of treatments in the most objective possible ways, taking care to minimize the likelihood that we will be misled by biases and the play of chance.

CLINICAL TRIAL

Let's see how a Phase 3 clinical trial is planned, what are the conditions needed to reach the best results.

- *First.* The protocol (plans) for clinical trials must be approved – scientifically and ethically by independent experts and lay people (Ethics Committee).
- *Second.* Two or more comparable groups of patients are needed to make a fair comparison between treatments, This is usually achieved by allocating patients at random to one of the two or more treatments being compared. If no treatment has yet been shown to be useful, the patients in one of the comparison group may receive no active treatment beyond usual care, or a placebo - a preparation that is inert but by appearance in all respects similar to the treatment being assessed.
- *Third.* The use of placebos can help to reduce the effects of distorting influences or pressures, often unintentional. Accordingly, when feasible, patients and those caring for them should not know which of the treatments (or placebo) they are receiving
- *Fourth.* Analyses of the data collected during clinical trials must be done as carefully as possible to minimize biases at this stage of the study.
- *Fifth.* Only very rarely does a single clinical trial provide evidence so persuasive that it can be used as a basis for practice. Accordingly, clinical trials should be repeated (replicated) to build up the evidence needed to provide a secure basis for treatment decisions.
- *Sixth.* To be statistically effective in comparison to placebo it is not necessary for drug approval: the drug should really improve the patient's condition. It must carefully evaluate both the therapeutic effects and side effects, that is harmful effects.

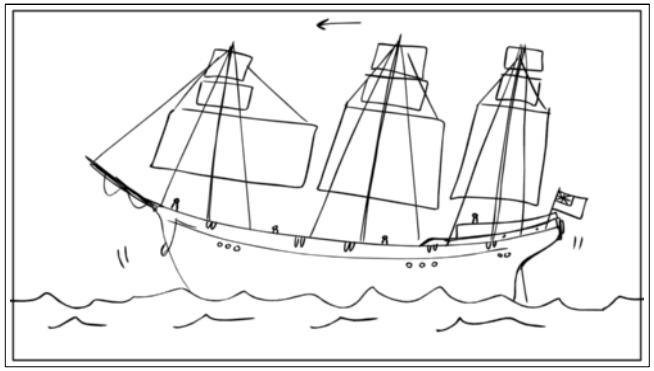
PITFALLS/TRAPS

It is important to know that behind every new treatment there are sometimes years of research, large investments, and powerful commercial interests. Even if the protocol and the principles of good clinical practice have been respected, there are influences that can distort the evidence in favour of a new, potentially very profitable treatment.

- When there are already other treatments available it is not ethical to withhold treatment or to use placebos. The comparison must be made with the best treatment available.
- So that the research can be used confidently to guide practice, patients who are often excluded from clinical trials – for example, children, elderly people, women, and other vulnerable populations – must be included
- Assessing the effects of treatments only on outcomes that are of little direct importance to patients (like some heart rhythm abnormalities, for example) are not helpful to patients and the clinicians looking after them. A treatment must be evaluated for its ability to reduce outcomes of importance to patients (like death from heart attack, for example), not only of the risk factors for patient-important outcomes.
- Finally, because new treatments are as likely to be worse as they are to be better than existing treatments, clinical trials must be designed to show whether a proposed new treatment is better than an existing treatment. Patients want to know whether a new treatment is actually better than existing treatments, not that research suggests that it may be no worse.

The health of all European citizens can be protected and promoted by health services informed by clinical research and clinical trials of treatments about which there are uncertainties. Trials done independently of the influences that too often distort the search for reliable evidence have a particularly important place in promoting this important research agenda.

Scene	Panel
1	1



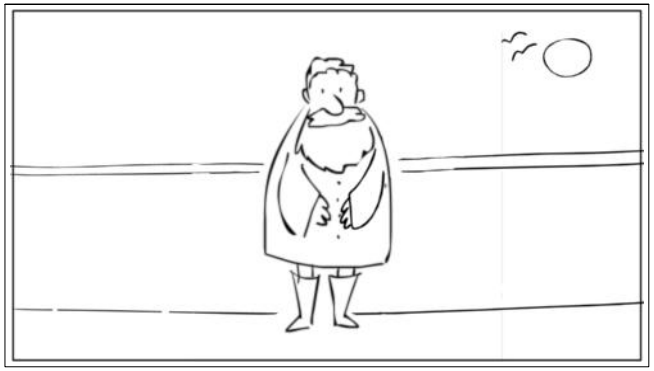
Dialogue

This is the story of a clinical trial that took place in 1747 on board a British Royal Navy ship.

Actions

A ship that is sailing in the sea

Scene	Panel
2	1



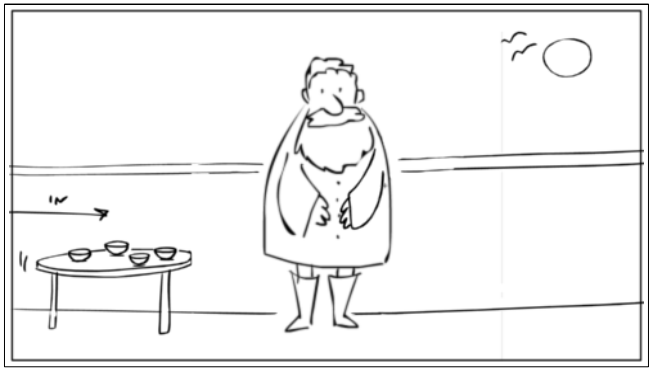
Dialogue

The ship's doctor to test which was the best way

Actions

A ship's doctor

Scene	Panel
2	2



Dialogue

to treat scurvy

Actions

Enters a table with bowls