Les activitats de seguiment de la recerca als CEIC

Societat Catalana de Farmacologia

Pilar Hereu
Servei de Farmacologia Clínica

10-6-2015

Generalitat de Catalunya
Departament de Salut

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

ICO
Institut Català d'Oncologia

Institut Català de la Salut
Hospital de Viladecans

Bellvitge
Hospital Universitari

CEIC Hospital de Bellvitge

Què fem?

- Avaluació projectes de recerca
  - Ètics
  - Legals
  - Metodològics
- Protocol + investigadors + aspectes locals

Com ho fem?

Autonomia

- Consentiment informat
- Confidencialitat

No maleficiència/beneficiència

- Relació benefici/risc
- Validesa científica
- Equip investigador

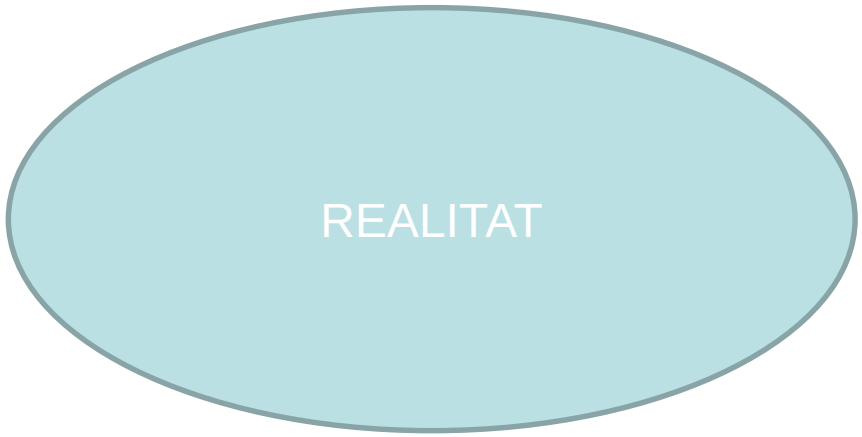
Justicia

- Criteris elegibilitat
- Protecció població vulnerable
- Compensació per danys

Protocol ≠ Realitat

Seguiment

Del protocol …. a la publicació



2316 *REAL DECRETO 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos.*

Artículo 10. *Funciones de los Comités Éticos de Investigación Clínica.*

Los Comités Éticos de Investigación Clínica desempeñarán las siguientes funciones:

a) Evaluar los aspectos metodológicos, éticos y legales de los ensayos clínicos que les sean remitidos, de conformidad con lo establecido en la sección 2.ª del capítulo IV.

b) Evaluar las modificaciones relevantes de los ensayos clínicos autorizados.

c) Realizar un seguimiento del ensayo, desde su inicio hasta la recepción del informe final.

DEPARTAMENT DE SALUT

DECRET
406/2006, de 24 d'octubre, pel qual es regulen els requisits i el procediment d'acreditació dels comitès d'ètica d'investigació clínica.

Article 4
Missió i funcions dels comitès

4.1 Els comitès d'ètica d'investigació clínica tenen com a missió vetllar per la protecció dels drets, seguretat i benestar dels éssers humans que participen en projectes de recerca que els puguin comportar algun risc físic o psicològic i donar-ne garantia pública, avaluant la correcció metodològica, ètica i legal d'aquests projectes i fent el seguiment de la seva realització en els centres inclosos en el seu àmbit d'actuació.

WMA

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

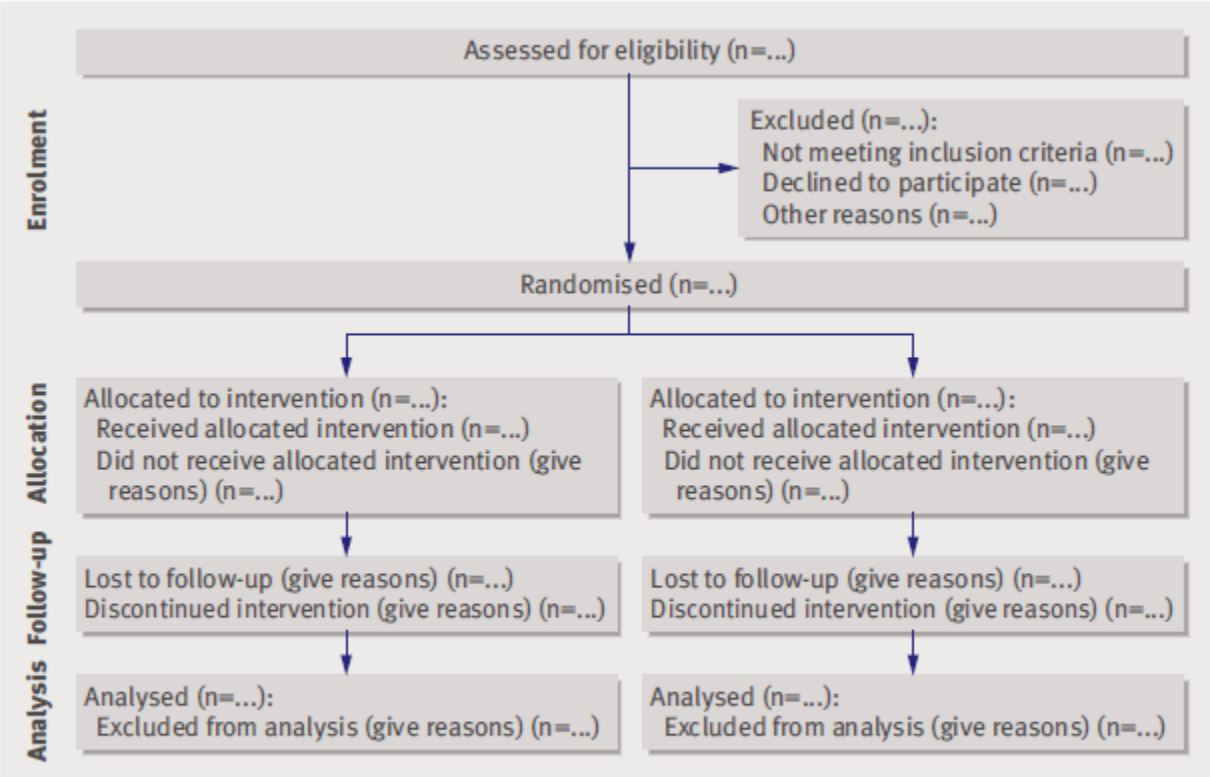


Fig 1 | Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)[52-54]

CDBI/INF(2011)2

Estrasburgo, a 7 de febrero de 2011

El Comité Director de la Bioética
(CDBI)

Guía para los Miembros de los Comités de Ética de Investigación

Figura 5.1 Funciones de los CEIs en el proceso de investigación

	Antes de comenzar la investigación		Después de que la investigación haya comenzado	
Fase de investigación	Planificación, diseño del proyecto	Revisión	Desarrollo	Fin de la investigación
Funciones	Proporcionar información a los investigadores *, cuando sea necesario	Evaluación ética de la propuesta de investigación	Seguimiento del proyecto de investigación en aspectos éticos concretos; posible reevaluación	Revisar los informes de los investigado-res*

European Textbook on Ethics in Research

EUROPEAN COMMISSION / European Research Area / Science in society

Besides their primary duty of the ethical review of research, research ethics committees often have other responsibilities related to their role as regulators of research. As noted above this may involve monitoring research, which can be carried out in a variety of ways such as requiring reports at regular intervals or at the end of a project, or even in some cases by carrying out *ad hoc* inspections or audits of research. Likewise, they are typically notified of adverse reactions and may have the responsibility of deciding whether a trial ought to be terminated or continued in the light of these reactions. These roles are typically remit-dependent and vary from country to country. ([46])

Research ethics committees might also have obligations to be vigilant for signs of fraud and scientific misconduct. ([47]) However, their powers to detect departures from an approved protocol are likely to be limited and resource dependent. Often scientific misconduct occurs after research has been conducted, and it would be rare for a research ethics committee to have any powers to intervene at that stage.

Al protocol …..seguiment

RESEARCH AND REPORTING METHODS | Annals of Internal Medicine

SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

Ethics and dissemination		
Research ethics approval	24	Plans for seeking REC/IRB approval
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

A la publicació … seguiment

CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials

Table 1 | CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[45 65])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	

Biomedical research: increasing value, reducing waste

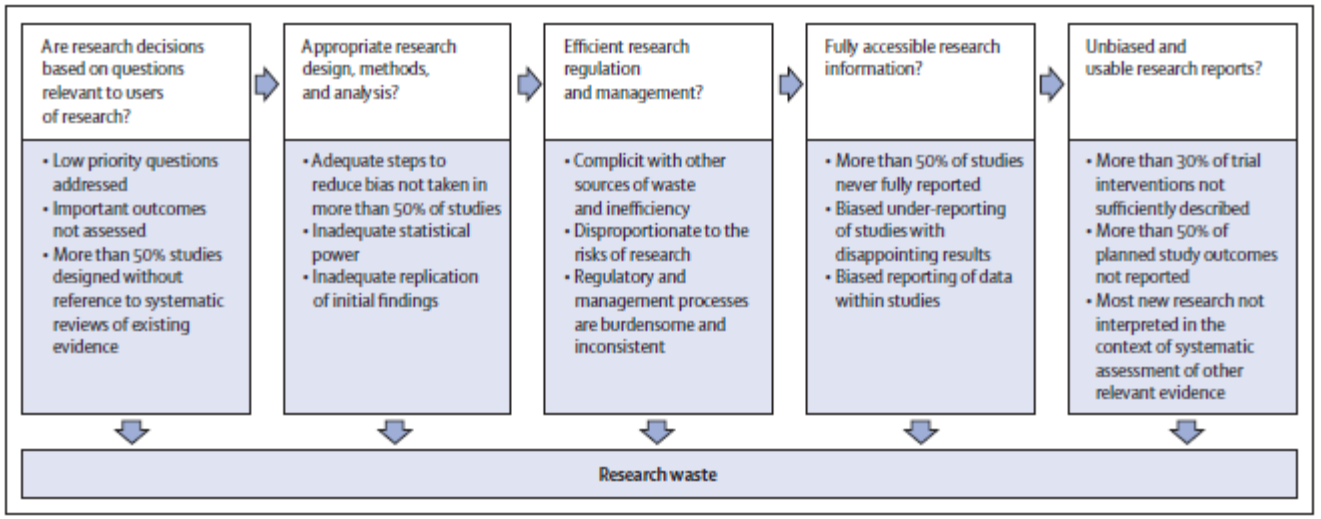


Figure: **Avoidable waste or inefficiency in biomedical research**

Research: increasing value, reducing waste 3

Increasing value and reducing waste in biomedical research regulation and management

Rustam Al-Shahi Salman, Elaine Beller, Jonathan Kagan, Elina Hemminki, Robert S Phillips, Julian Savulescu, Malcolm Macleod, Janet Wisely, Iain Chalmers

***Panel 2*: Features that research regulation and review should require**

- Show evidence, by reference to systematic reviews of relevant existing research evidence, that proposed additional research will address important continuing uncertainties
- Proportionate assessment of applications and comparison of potential benefits with any harm envisaged for research participants, additional to whatever would be expected during the health care that they would otherwise receive
- Potential research participants should be given, at the time of recruitment, a summary of existing evidence from systematic reviews (including, but not restricted to, evidence from clinical trials) about the possible risks and benefits of their participation, which is tailored to the nature and context of their illness
- Potential participants to be free to consent to research entailing reasonable, but more than minimal, risk (in some circumstances, even when consent cannot be obtained, such as in emergencies)
- Support for opt-out systems (or, in some rare circumstances, non-consensual systems) for collection of deidentified data from medical records, blood samples, and discarded tissue
- Registration of protocols for clinical trials in the public domain at trial inception
- Researchers, research funders, and research institutions to make their protocols and research results publicly accessible
- Provision, for every participant who wishes to receive them, of reports of results (including treatment received) and future available options
- Audit by research ethics services and other regulators of the conduct of research and reporting of results
- Appropriate randomised evaluations of research regulation and management strategies

Investigación clínica y bioética

Análisis descriptivo de los hallazgos en auditorias de ensayos clínicos (2001–2007)

Descriptive analysis of audit findings in clinical trials (2001–2007)

Ana Aldea [a,b,*,◆], Juan Francisco Tosca [c], Ernesto Vera [d] y Carmen Tristán [d]

[a] *Dirección General de Farmacia, Servicio Canario de Salud, Hospital Universitario de Canarias, Tenerife, España*
[b] *Unidad Central de Apoyo a la Investigación Clínica y Ensayos Clínicos, Consorcio de Apoyo a la Investigación Biomédica En Red (CAIBER), Madrid, España*
[c] *Inspección de Servicios Sanitarios, Conselleria de Sanitat, Valencia, España*
[d] *Servicio de Inspección de Buena Práctica Clínica, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, España*

Tabla 2
Hallazgos de inspecciones en EE. UU., Japón y España

Desviaciones	EE. UU. (1997), Saito et al[4]	Japón (1997–1999), Saito et al[2–4]	Japón (2002–2003), Saito et al[2–4]	España (2002–2007)
	N.° de inspecciones con hallazgos, %			
Falta de adherencia al protocolo	25	14,7	48,2	36,4
Falta de datos/mala recogida de datos en CRD	20	43,6	16	45,4
Consentimiento informado	21	1,8	4,7	22,7
Contabilidad inadecuada de medicación	13	4,7	1,2	ND
Problemas relacionados con el archivo	ND	11,1	17,5	50
Falta de listado de investigadores colaboradores	ND	4,1	ND	50
Falta en archivo de informes favorables del CEIC de enmiendas	ND	2,4	ND	22,5

CEIC: Comité Ético de Investigación Clínica; CRD: cuaderno de recogida de datos; ND: no disponible.

….. Com ho fem en el seguiment?

Autonomia

- Consentiment informat
- Confidencialitat

No maleficiència/beneficiència

- Relació benefici/risc
- Validesa científica
- Equip investigador

Justicia

- Criteris elegibilitat
- Protecció població vulnerable
- Compensació per danys

MEMORIA CEIC
HOSPITAL UNIVERSITARI DE BELLVITGE
ANY 2014

L'Hospitalet de Llobregat (Barcelona)

Hospital Universitari de Bellvitge
Comitè Ètic d'Investigació Clínica (CEIC)

Nom centre	*AC*	*IC PS*	*EPA*	*MB*	*A INV*	*ALTRES*	*TOTAL*
Hospital Universitari de Bellvitge[1]	78	6	55	55	3	128	325
Institut Català d'Oncologia L'Hospitalet (ICO)	85	4	7	53	-	46	195
Institut d'Investigació Biomèdica de Bellvitge (IDIBELL)[2]	1	-	-	59	-	4	64
Hospital de Viladecans	1	-	3	-	-	4	8
Hospital d'Igualada	1	1	1	-	-	5	8
Hospital Comarcal de l'Alt Penedès	-	-	-	-	-	1	1
Biobanc HUB-ICO-IDIBELL	-	-	-	18	-	-	18
Fundació Sociosanitària de Barcelona	-	1	-	-	-	-	1
TOTAL[3]	166	12	66	185	3	188	620

Taula II

1 Inclou la Unitat docent Universitat de Barcelona (UB) Campus Bellvitge.
2 Centre no sanitari
3 Segons la nota informativa de la Direcció General de Recursos Sanitaris, si un projecte de recerca s'ha dut a terme en diferents centres, s'ha computat per a cadascun dels centres. La quantitat real de propostes és de 612.

Bellvitge Hospital Universitari

Institut Català de la Salut

Generalitat de Catalunya
Departament de Salut

PROCEDIMIENTOS NORMALIZADOS DE TRABAJO
CEIC HOSPITAL UNIVERSITARI DE BELLVITGE

Versión de fecha 22/03/12

Què fem de seguiment al ceic HUB?

- Revisió esmenes rellevants al protocol
- Revisió dades de seguretat:
  - Informes de seguretat ad-hoc
  - SAE centre
  - informes seguretat
- Desviacions de protocol
- Aturades prematures
- Altres:
  - Seguiment pòlisses assegurances
  - Formació BPC
  - Informes anuals/ Informes finals
  - Data inclusió primer pacient

2014

- Notificacions TOTALS al sistema informacio del ceic 4019
  - Esmenes 652
  - Seguretat ad hoc 30
  - Desviacions de protocols 53
  - Aturades prematures 31

Esmenes rellevants

Rellevant: Que afecta la validesa estudi o seguretat del pacient

Tipus de projecte d'investigació biomèdica	*Núm. de esmenes rellevants avaluades l'any 2014*
Assaigs clínics amb medicaments i/o producte sanitari	598
Estudis postautorització observacionals amb medicaments	16
Altres projectes d'investigació i projectes de recerca amb mostres biològiques d'origen humà	38
Total	652

Taula VI

Seguretat

- SUSAR i RAGI
- Informació de seguretat ad-hoc
- Informes de seguretat anuals

Desviacions protocols

- Classificació i notificacio segons AEMPS
- Poc descrits a les publicacions

Sweetman and Doig *Trials* 2011, **12**:214
http://www.trialsjournal.com/content/12/1/214

TRIALS

RESEARCH Open Access

Failure to report protocol violations in clinical trials: a threat to internal validity?

Elizabeth A Sweetman[1] and Gordon S Doig[1,2*]

Table 4 Protocol violation reporting and protocol violation frequency.

Protocol Violation Type	Percent (number) of trials	Proportion of Enrolled Participants with PVs Median (range) Calculated from trials with Explicit Reporting
Enrolment PVs		
Explicit reporting	12.5% (10/80)	0.8% (1.6% to 9.1%)
Incomplete reporting	8.8% (7/80)	
Absent	78.8% (63/80)	
Randomisation PVs		
Explicit reporting	8.8% (7/80)	0.7% (0.04% to 7.7%)
Incomplete reporting	1.3% (1/80)	
Absent	90.0% (72/80)	
Study Intervention PVs		
Explicit reporting	21.2% (17/80)	1.3% (0% to 13.2%)
Incomplete reporting	21.2% (17/80)	
Absent	57.5% (46/80)	
Patient compliance PVs		
Explicit reporting	47.5% (38/80)	7% (0.2% to 87%)
Incomplete reporting	25.0% (20/80)	
Absent	27.5% (22/80)	
Data Collection PVs		
Explicit reporting	21.3% (17/80)	1.7% (0.0% to 16.1%)
Incomplete reporting	18.8% (15/80)	
Absent	60.0% (48/80)	

Abbreviations: PV - protocol violations.

Aturades prematures

2316 *REAL DECRETO 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos.*

2. En caso de terminación anticipada, en el plazo de 15 días el promotor remitirá a la Agencia Española de Medicamentos y Productos Sanitarios y a los Comités Éticos de Investigación Clínica implicados un informe que incluya los datos obtenidos hasta el momento de su conclusión anticipada, así como los motivos de ésta, y en su caso las medidas adoptadas en relación con los sujetos participantes en el ensayo.

SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials

An-Wen Chan,[1] Jennifer M Tetzlaff,[2] Peter C Gøtzsche,[3] Douglas G Altman,[4] Howard Mann,[5] Jesse A Berlin,[6] Kay Dickersin,[7] Asbjørn Hróbjartsson,[3] Kenneth F Schulz,[8] Wendy R Parulekar,[9] Karmela Krleža-Jeric,[10] Andreas Laupacis,[11] David Moher[2 10]

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Contined

Section/item	ItemNo	Description
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials

Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[42])

Aturades prematures AC 2014

- N=31 assaigs clínics amb medicaments

  – CEIC Referència N=9
  – Presenten Annex D Fi assaigs n= 24 (77%)
    - Hi ha 2 aturades reclutament temporal annex 1c
  – Anys des de sol·licitud EudraCT: 1,9 (0-8)
  – Promotor IF n= 26 (83%)
  – Indicació Oncologia n=16 (51%)

Aturades prematures AC 2014 n=31

- AC amb medicament en investigació
  - Comercialitzat SI n= 11
  - Químic si n= 24
- Fases
  - I n= 3
  - II n=10
  - III n= 14
  - IV n=1
  - Extensió 3

Aturades prematures AC 2014 n=31

- Motius aturades
  - Reclutament sol n= 5
  - Reclutament+ interes empresa n= 2
  - Interès empresa n= 6
  - Eficàcia + n= 2
  - Eficàcia - n= 10
  - Seguretat n= 2
  - Subministrament MI n=1
  - Poc clar n= 3

Aturades prematures AC 2014 n=31

- Repercusions aturades
  - Canvi valoracio benefici/risc si n=1
  - Aturada desenvolupament
    - Si global n= 8
    - Si en indicacio n= 2

Aturades prematures AC 2014 n=31

- Gestió de l'aturada
  - Es preveu informar als pacients?
    - SI n=9
  - Es dona FIP?
    - Si n=3

Original Investigation

Prevalence, Characteristics, and Publication of Discontinued Randomized Trials

Benjamin Kasenda, MD; Erik von Elm, MD, MSc; John You, MD, MSc; Anette Blümle, PhD; Yuki Tomonaga, MSc; Ramon Saccilotto, MD, MSc; Alain Amstutz, BSc; Theresa Bengough, BSc; Joerg J. Meerpohl, MD; Mihaela Stegert, MD; Kari A. O. Tikkinen, MD, PhD; Ignacio Neumann, MD, MSc; Alonso Carrasco-Labra, MD, MSc; Markus Faulhaber, MD, MSc; Sohail M. Mulla, BSc; Dominik Mertz, MD, MSc; Elie A. Akl, MD, PhD, MPH; Dirk Bassler, MD, MSc; Jason W. Busse, DC, PhD; Ignacio Ferreira-González, MD, PhD; Francois Lamontagne, MD, MSc; Alain Nordmann, MD, MSc; Viktoria Gloy, PhD; Heike Raatz, MD, MSc; Lorenzo Moja, MD, MSc; Rachel Rosenthal, MD, MSc; Shanil Ebrahim, PhD; Stefan Schandelmaier, MD; Sun Xin, PhD; Per O. Vandvik, MD, PhD; Bradley C. Johnston, PhD; Martin A. Walter, MD; Bernard Burnand, MD, MSc; Matthias Schwenkglenks, PhD; Lars G. Hemkens, MD; Heiner C. Bucher, MD, MPH; Gordon H. Guyatt, MD, MSc; Matthias Briel, MD, MSc

JAMA. 2014;311(10):1045-1051. doi:10.1001/jama.2014.1361

N= 1017 ACs

- 253 (24%) son discontinuats
  - 37% s'informa al CEIC
- Motius:
  - 1º poc reclutament (101/1017, 10%)
  - 2º raons administratives (3,8%)
  - 3º futilitat (3,6%)
- Els discontinuats es publiquen menys

Table 2. Prevalence of Randomized Clinical Trial (RCT) Discontinuation and Reported Reasons for Discontinuation

	No. (%) [95% CI]									
	RCTs Involving Patients				RCTs Involving Healthy Volunteers				All	
	Sponsorship				Sponsorship					
	Industry (n = 551)	Investigator (n = 343)	All (n = 894)	Full Journal Publication (n = 530)	Industry (n = 86)	Investigator (n = 37)	All (n = 123)	Full Journal Publication (n = 37)	All (n = 1017)	Full Journal Publication (n = 567)
Completion status										
Completed	394 (71.5) [68.1-75.2]	181 (52.8) [47.3-58.1]	575 (64.3) [61.1-67.4]	417 (78.7) [75.0-82.0]	81 (94.2) [86.3-97.8]	28 (75.7) [58.4-87.6]	109 (89.0) [81.3-93.4]	37 (100.0) [88-100]	684 (67.3) [64.3-70.1]	454 (80.1) [76.6-83.2]
Discontinued	119 (21.6) [18.3-25.3]	130 (37.9) [32.8-43.3]	249 (27.9) [25.0-30.9]	113 (21.3) [18.1-25.0]	1 (1.2) [0.0-7.2]	3 (8.1) [2.1-23.0]	4 (3.3) [1.0-8.6]	0 [0.0-11.7]	253 (24.9) [22.3-27.6]	113 (20.0) [16.9-23.4]
Unclear	38 (6.9) [5.0-9.4]	32 (9.3) [6.6-13.0]	70 (7.8) [6.2-9.8]	0 [0.0-0.9]	4 (4.7) [1.5-12.1]	6 (16.2) [6.8-32.7]	10 (8.1) [4.2-14.8]	0 [0.0-11.7]	80 (7.7) [6.3-9.71]	0 [0.0-0.8]
Reason for discontinuation										
Poor recruitment[a]	40 (7.3) [5.3-9.8]	60 (17.5) [13.7-22.0]	100 (11.2) [9.2-13.5]	40 (7.5) [5.5-10.2]	0 [0.0-5.3]	1 (2.7) [0.1-15.8]	1 (0.8) [0.04-5.1]	0 [0.0-11.7]	101 (9.9) [8.2-12.0]	40 (7.1) [5.1-9.6]
Futility[b]	25 (4.5) [3.0-6.7]	12 (3.5) [1.9-6.2]	37 (4.1) [3.0-5.7]	18 (3.4) [2.1-5.4]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	37 (3.6) [2.6-5.0]	18 (3.2) [1.9-5.1]
Administrative reasons[c]	20 (3.6) [2.3-5.7]	16 (4.7) [2.8-7.6]	36 (4.0) [2.9-5.6]	8 (1.5) [0.7-3.1]	1 (1.2) [0.0-7.2]	2 (5.4) [0.9-19.5]	3 (2.4) [0.6-7.5]	0 [0.0-11.7]	39 (3.8) [2.8-5.3]	8 (1.4) [0.7-2.9]
Harm	17 (3.1) [1.9-5.0]	7 (2.0) [0.9-4.3]	24 (2.7) [1.8-4.0]	12 (2.3) [1.2-4.0]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	24 (2.4) [1.6-3.5]	12 (2.1) [1.2-3.8]
Unknown reason[d]	6 (1.1) [0.4-2.5]	18 (5.3) [3.2-8.3]	24 (2.7) [1.8-4.0]	21 (4.0) [2.6-6.0]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	24 (2.4) [1.6-3.5]	21 (3.7) [2.4-5.6]
Benefit	2 (0.4) [0.06-1.5]	7 (2.0) [0.9-4.2]	9 (1.0) [0.5-2.0]	9 (1.7) [0.8-3.3]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	9 (0.9) [0.4-1.7]	9 (1.6) [0.8-3.1]
External evidence	6 (1.1) [0.4-2.5]	2 (0.6) [0.1-2.3]	8 (0.9) [0.4-1.8]	2 (0.4) [0.0-1.5]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	8 (0.8) [0.4-1.6]	2 (0.4) [0.1-1.4]
Lack of funding	1 (0.2) [0.01-1.2]	4 (1.2) [0.4-3.2]	5 (0.6) [0.2-1.4]	0 [0.0-0.9]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	5 (0.5) [0.2-1.2]	0 [0.0-0.8]
Other	2 (0.4) [0.06-1.5]	4 (1.2) [0.4-3.2]	6 (0.7) [0.3-1.5]	3 (0.6) [0.2-1.7]	0 [0.0-5.3]	0 [0.0-11.7]	0 [0.0-3.8]	0 [0.0-11.7]	6 (0.6) [0.2-1.3]	3 (0.5) [0.2-1.6]

[a] Some trials had an additional reason for discontinuation: benefit (n = 1), futility (n = 2), and other reasons (n = 3).

[b] Includes randomized trials with adaptive designs that have been stopped after the 1st (n = 5) or 2nd stage (n = 1).

[c] Includes strategic decisions from companies, consequence of new requirements from regulatory bodies, and change of workplace of principal investigators.

[d] Reasons for not achieving 90% of target sample size remained unclear.

Factors associats a discontinuació per poc reclutament

- Promotor no és IF
- Major mida de la mostra

Factors no associats

- Nº centres
- Tipus de disseny estudi
- Control amb placebo
- Planificacio reclutament
- Suport logístic o metodològic

Comitè de Monitorització de dades

Metodología

validesa científica

precisió estimació

Etica

Valoració benefici/risc pacient

Autonomia del pacient

The dilemma of data-safety monitoring: provision of significant new data to research participants

Jeffery Peppercorn, William G Buss, Norm Fost, Paul A Godley

Panel 1: Guiding questions for analysis of action after interim analyses by data-monitoring committees

- What is the nature of the harm or benefit that the data-monitoring committee must consider in deciding whether to report information?
- What are the costs to research participants and to future patients if no further information is obtained from the randomised controlled trial?
- Is the withholding of this information by the data-monitoring committee consistent with the consent and consequent reasonable understanding of research participants?

Panel 2: Questions to address to improve participant's understanding of the role of data-monitoring committees for informed consent

Information to convey to potential research participants

What is a data-monitoring committee?

- It is a group of independent experts, distinct from the investigators and sponsors of the research
- It has no direct stake in the completion of the study or its outcomes
- It holds periodic meetings to review and discuss current study data

What factors does the data-monitoring committee consider when reviewing new information from a trial?

- The nature and magnitude of risks and benefits identified in the course of the study
- The likelihood that any benefits to participants are related to the experimental intervention
- The likelihood that any risks to participants are related to the experimental intervention
- The nature of the disease being studied and whether the study is for prevention or treatment
- The nature of the experimental intervention

What factors does the data-monitoring committee regard as important when making decisions about sharing new information with participants and investigators?

- The safety and interests of the participants
- The obligation to share important new information with participants and researchers
- The scientific validity of potentially important new information
- The effect that stopping the study will have on the ability to answer important scientific questions affecting future patients

Què fan altres CEIC?

CEIC Vall d'Hebron
Consentiment informat

Contemporary Clinical Trials 31 (2010) 443–446

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Short communication

Consent in clinical trials: What do patients know?

Pilar Hereu [a,*], Eulàlia Pérez [a,b,c], Inma Fuentes [a,b], Xavier Vidal [a,b,c], Pilar Suñé [d], Josep Maria Arnau [a,b,c]

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ABSTRACT

Objective: To assess participants' knowledge of key aspects about the clinical trials in which they are enrolled, describe the consent process, and assess the importance that investigators give to various aspects of trial information when verbally informing candidates.
Design: Prospective study based on a structured questionnaire interview of participants within 3 months after trial enrollment and an anonymous questionnaire sent to clinical trial investigators.
Subjects: A total of 140 participants included in 40 clinical trials were interviewed, and 51 investigators answered the questionnaire.
Results: The formal steps to obtain informed consent were usually carried out. Participants were aware of the purpose of the trial and the right to discontinue participation, but only 23% knew that treatment was randomly allocated, 57% knew they might receive a placebo, and 42% was aware that adverse effects could occur. Patients who had read the information sheet had better knowledge of most aspects, except for the risk of adverse effects. The investigators considered that compensation, insurance coverage, possibility of receiving a placebo, and treatment allocation were the least important aspects of the trial when informing candidates for participation.
Conclusions: Although the formal steps for obtaining informed consent were usually carried out, a relevant percentage of patients included in clinical trials were unaware of important aspects of their participation. Patients showed more limited knowledge about the same points that investigators considered less important when informing potential participants. Deferring signature on the consent form and encouraging reading of the information sheet may improve participants' knowledge about clinical trials.

Aspectos evaluados	Sí conoce %
Posibilidad de retirada	88
Objetivo	74
Posibilidad de recibir placebo	57
Posibilidad efectos adversos	42
Seguro del estudio	35
Asignación tratamiento al azar	23

CEIC Parc Taulí

Seguiment del projecte d' investigació

Codigo CEIC 2001109 Promotor **UAB**

Codi Promotor

Títol del projecte

Investigador Principal **ABAD GAIRÍN CARLOS**

Situació	
0	-
1	Pendent d'inici
2	Suspès abans d'inici
3	Suspès després d'inici
4	En curs, inclusió oberta
5	En curs, inclusió tancada
6	Finalitzat
7	Altres

Motius de suspensió o de tancament prematur

ACTIU

Data prevista tancament periode reclutament (si procedeix)

Data prevista finalització completa de l'estudi: 31/12/2005

Considera que l' evidencia actual sobre el tema permet la continuació de l'estudi en les mateixes condicions que les establertes inicialment? ☐ Si ☐ No

En caso negatiu , descriu els motius i els cambis proposats:

FINALITZAT

Data real finalització completa de l'estudi:

Número de pacients en el centre. Pacients previstos inicials: 10

Pacients inclosos:

En el caso de diferències (sota reclutament..), explicar breument els motius:

S' ha redactat informe final? ☐

Ha derivat alguna publicació? ☐ (adjuntar separates)

S' ha fet difusió parcial o total en algún congres, jornades .... ☐ (adjuntar separates)

AFEGIR ALTRA INFORMACIÓ D' INTERÈS QUE VOLGUEU APORTAR (actualizacions de col·laboradors, etc..)

SABADELL a jueves, 01 de febrero de 2007

Med Clin (Barc). 2012;139(4):176–179

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Investigación clínica y bioética

Revisión de las observaciones más frecuentes en la hoja de información al paciente para ensayos clínicos

A review of the most frequent objections made to patient information sheets of clinical trials

María López-Parra, Coloma Moreno-Quiroga * y Javier Lechuga-Pérez

Comitè d'Ètica d'Investigació Clínica, Fundació Parc Taulí, Corporació Sanitària Parc Taulí, Institut Universitari Parc Taulí-Universitat Autònoma de Barcelona, Campus d'Excelència Internacional, Bellaterra, Barcelona, España

Tabla 1
Puntos valorados en las hojas de información al paciente y su agrupación

	Lista de comprobación extendida	Lista de comprobación agrupada
1	*En la forma*	Forma
1.1	¿Consta de documento escrito?	
1.2	¿Consta dar un copia al enfermo?	
1.3	¿Consta un lugar para la firma del paciente o de su representante?	
1.4	¿Hay palabras técnicas de difícil comprensión?	
1.5	¿Hay abreviaturas técnicas?	
1.6	Los apartados (objetivos,. . .) están claramente delimitados	
1.7	¿El tipo de letra es legible?	
1.8	¿Es extenso? (superior a 10 páginas)	
2	*En el contenido*	Contenido
2.1	El objetivo de la investigación	Metodología
2.2	Los procedimientos que son experimentales	
2.3	La metodología de la investigación	
2.4	Si se utiliza placebo, en qué consiste. ¿Es un trastorno banal?	
2.5	El tiempo de duración en el estudio	
2.6	N° de pacientes aproximado que se prevé que participen	
2.7	Los beneficios nuevos respecto a los tratamientos habituales (mejoría de salud, confort, posología, etc.)	Beneficios y riesgos
2.8	Los riesgos o molestias previsibles para el paciente	
2.9	Existencia de riesgos que no son previsibles	
2.10	En caso de aparición de nuevos datos en el curso de la investigación estos serán comunicados al paciente	
2.11	Medidas anticonceptivas/riesgos para el embarazo	
2.12	Quién accederá a la información (promotor, autoridades, . . .)	Confidencialidad
2.13	El deber de confidencialidad en todos los que pueden acceder a la información	
2.14	La diferencia con la asistencia habitual (si se harán más pruebas, visitas, etc.)	Información general que
2.15	El tratamiento alternativo en caso de no participar	no altera la metodología
2.16	Posibilidad de recibir más información	
2.17	A quién se puede pedir más información	
2.18	El nombre del investigador principal	
2.19	Información sobre la póliza de seguros	
2.20	Información del tratamiento en caso de lesión	
2.21	Compensación económica al paciente	
2.22	Cumple la Ley 14/2007	Información Ley 14/2007
2.23	Participación voluntaria	Voluntariedad
2.24	Ausencia de perjuicios en caso de no participar	
2.25	Posibilidad de retirada del estudio sin dar explicaciones y sin ningún perjuicio	
2.26	Expresiones tendenciosas para la participación	

CEIC H Clínic
Publicació resultats

RESEARCH LETTERS

Role of a research ethics committee in follow-up and publication of results

Judit Pich, Xavier Carné, Juan-Alberto Arnaiz, Begoña Gómez, Antoni Trilla, Juan Poblet

Follow-up of clinical trials is a commitment rarely fulfilled by research ethics committees (RECs). We assessed the output of clinical trials submitted in 1997 to our REC, and talked to principal investigators, sponsors, contract research organisations, or a combination of these. During 1997, our REC reviewed 146 clinical trials, and approved 158. The recruitment rate was lower than expected in 45% (64/143) of all initiated clinical trials; 64% (92/143) were finished in accordance with protocol. 3 years after, the results of only 21% (26/123) of finished clinical trials were published in peer-reviewed journals, rising to 32% (38/123) if in-press articles were included. RECs should devote more effort and resources to assess public dissemination of results of clinical trials.

Lancet 2003; **361**: 1015–16
See Commentary page 978

The main role of research ethics committees (RECs) is to assess both the scientific and ethical aspects of submitted protocols. RECs are responsible not only for approval of the protocol and its amendments but also for follow-up and monitoring of the trial until its closure.[1] This last commitment is rarely fulfilled because of lack of time and resources assigned to RECs.

There has been considerable debate in the medical community about the role and effectiveness of the REC reviewing process. A major concern relates to the outcome of results of clinical trials. Findings of studies must be publicly available and disseminated within an appropriate timescale once they come to an end. If information gathered in clinical trials is not publicly disseminated, an important ethical requirement is not fulfilled.[2]

The Hospital Clínic ethics committee (HCEC) is the REC to which most clinical-trial protocols are submitted for approval in Spain (around 250 per year). The objective of our survey was to assess the outcome of all protocols submitted to the HCEC during 1997.

We judged a 3-year period was long enough to assess the final outcome of most approved protocols. All information included in the HCEC clinical trials' database about protocols submitted in 1997 was reviewed, and principal investigators were sent a standard questionnaire. When necessary, sponsors, contract research organisations (CROs), or both were also interviewed. This survey was approved by the HCEC.

Data collection was done from April, 2001, until October, 2001. Overall, 63 different principal investigators and 30 pharmaceutical-industry sponsors were approached. In a third of clinical trials, a CRO had a role.

In 1997, 534 clinical-trial protocols were submitted to the Spanish Medicines Agency (SMA).[3] During that year the HCEC reviewed 166 clinical trials, and finally approved 158 (95%). Three trials (2%) were phase 1, 29 (18%) phase 2, 94 (59%) phase 3, and 32 (20%) phase 4. Of all clinical trials, 141 (89%) were sponsored by pharmaceutical industry, and 142 (90%) were multicentre studies.

We finally assessed 154 protocols, because of absence of information in four (figure). 11 (7%) clinical trials never started because of delay in obtaining permission from the SMA (n=5), sponsor withdrawal (2), change of surgical technique (1), safety reasons (1), absence of efficacy from previous studies (1), and because the SMA did not grant official permission (1).

In 64 (45%) of the remaining 143 clinical trials, the level of recruitment was lower than expected, in 39 (27%) was as expected, and in 34 (24%) was higher than expected. In one (1%) clinical trial the recruitment period was not closed, and no information was available for five (3%).

A total of 123 clinical trials (86%) had finished, and 20 (14%) were still in progress, by October, 2001. In 31 clinical trials the study was prematurely stopped (figure). Reasons were: efficacy lower than expected (11), recruitment rate lower than expected (11), safety problems (7), study drug released into market (1), and positive results of other trials being reported (1). In only 14% of closed clinical trials had the sponsor spontaneously submitted the final report to the REC.

Of the 143 clinical trials that started, 39 (27%) presented their final results to scientific meetings. In 26 (21%) of 123 trials that closed, results were published in biomedical journals included in science citation index, resulting in 29 published papers (table). According to sponsors' latest information, we recorded an overall publication rate of 31%

Fate of clinical trials approved in 1997, by October, 2001

Journal	Articles
Advances in Therapy	1
AIDS (LONDON)	1
American Journal of Respiratory and Critical Care Medicine	1
Chest	1
Circulation	1
Diabetes	1
Diabetes Care	3
Diabetes, Nutrition, and Metabolism	1
Diabetic Medicine	1
European Journal of Cancer	1
European Journal of Heart Failure	1
Experimental and Clinical Endocrinology and Diabetes	1
Gastroenterology	1
Journal of the American College of Cardiology	1
Journal of Heart Valve Disease	2
Journal of Hypertension	1
Lancet	5
Neurology	1
New England Journal of Medicine	3
Transplantation	1

Biomedical journals in which articles with clinical trial results were published

ICB digital

nº 72
mayo-junio de 2011

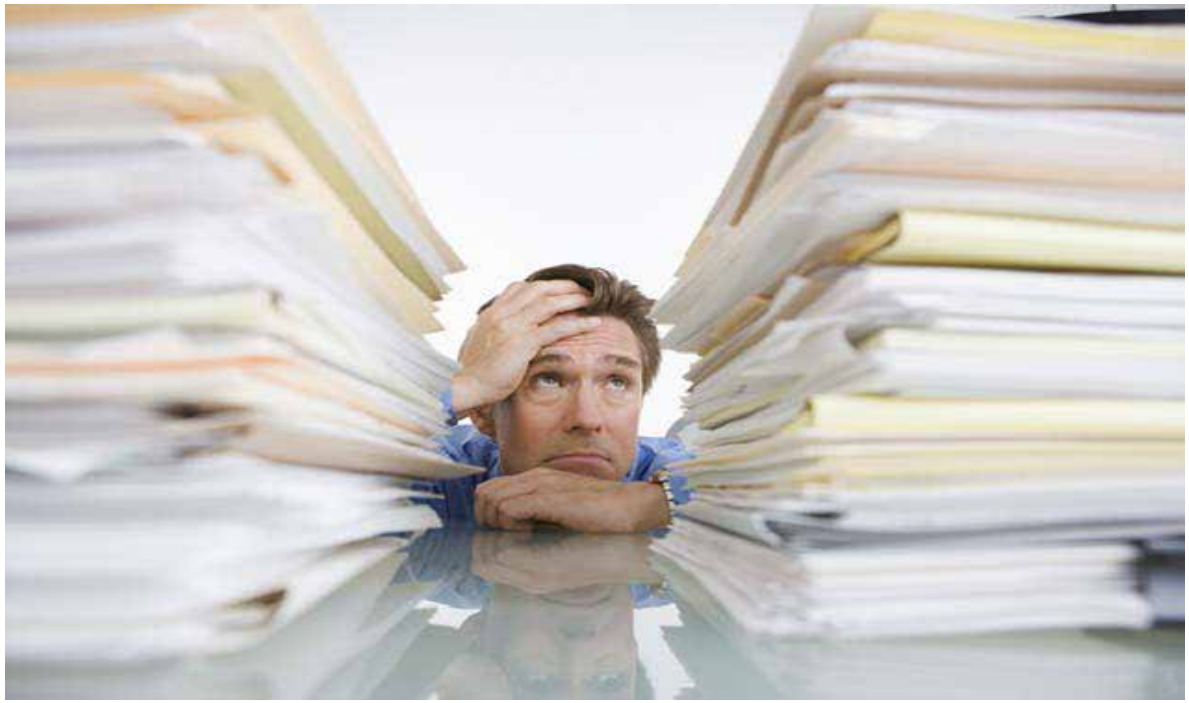
artículo original

Satisfacción de los promotores de ensayos clínicos con el funcionamiento de un comité ético de investigación clínica.

Tabla 1. Encuesta de satisfacción enviada a los promotores de ensayos clínicos

	NIVEL DE ACUERDO 1 = Totalmente en desacuerdo 2 = En desacuerdo 3 = Ni de acuerdo ni en desacuerdo 4 = De acuerdo 5 = Totalmente de acuerdo						IMPORTANCIA 1 = Muy Poco importante 2 = Poco importante 3 = Importancia media 4 = Bastante importante 5 = Muy importante				
1. El funcionamiento y procedimientos de trabajo del CEICA han sido transmitidos con claridad	1	2	3	4	5		1	2	3	4	5
2. En cuanto a la documentación necesaria para que el Ensayo Clínico pueda ser evaluado:											
2a. a) Está claramente especificada	1	2	3	4	5		1	2	3	4	5
2b. b) En caso de que esté incompleta, la documentación pendiente necesaria para iniciar el proceso de evaluación se comunica con claridad	1	2	3	4	5		1	2	3	4	5
3. El CEICA me hace llegar toda aquella información/documentación que le solicito	1	2	3	4	5		1	2	3	4	5
4. El seguimiento de los Ensayos Clínicos se realiza adecuadamente durante el desarrollo de los mismos	1	2	3	4	5		1	2	3	4	5
5. Es fácil contactar con el personal del CEICA	1	2	3	4	5		1	2	3	4	5
6. El personal de contacto del CEICA atiende con amabilidad	1	2	3	4	5		1	2	3	4	5
7. Las incidencias y cuestiones planteadas son resueltas con claridad	1	2	3	4	5		1	2	3	4	5
8. Las incidencias y cuestiones planteadas son resueltas con agilidad	1	2	3	4	5		1	2	3	4	5
9. La valoración global otorgada al funcionamiento del CEICA es buena	1	2	3	4	5						

75% considera CEIC fa seguiment de manera adequada



Algunes reflexions

Centrar l’objectiu en la protecció pacient

No duplicar esforços CEIC vs AEMPS

Prioritzar esforços al CEIC

Discriminar el que és rellevant

Gracies

Kasenda et al. BMC Medical Research Methodology 2012, 12:131
http://www.biomedcentral.com/1471-2288/12/131

BMC
Medical Research Methodology

STUDY PROTOCOL Open Access

Learning from failure - rationale and design for a study about discontinuation of randomized trials (DISCO study)

Table 2 Potential risk factors and protective factors for trial discontinuation due to slow recruitment

Modifiable factors		Non-modifiable Factors	
Risk	**Protective**	**Risk**	**Protective**
Burdensome data collection at recruiting sites	Support from a methods centre, clinical trials unit, or contract research organization	Placebo control	Active treatment as control
No professional staff at recruiting centres to manage the trial	Paid local staff at recruiting centres, dedicated central trial coordinator, patient involvement in trial planning and/or conduct	No external funding	Externally funded or fully Industry sponsored
No projection of recruitment rates	Projection of patient recruitment based on e.g. pilot trial applying the full protocol or other checks for eligible patient volume	Long duration of follow-up	Short duration of follow-up / High community interest in research topic (e.g. new technology or new treatment)
No consideration of recruitment strategies	Consideration of recruitment support strategies (e.g. regular visits/audits by PI; specific training held for recruiting staff; regular progress reports; posters and information leaflets etc.)	No research network, low trial experience	Experienced PI/steering committee/ network of recruiting centres for RCTs
Single centre trial	Multicentre trial	Equivalence/non-inferiority design	Intervention only available through trial participation
Low motivation for recruiting sites	Financial incentives for recruiting staff and participants	Critically ill or paediatric patients as target population	Trial experience with certain vulnerable trial populations

Table 3. Factors Associated With Discontinuation of Randomized Clinical Trials (RCTs) Due to Poor Recruitment in RCTs Involving Patients[a]

Characteristics	RCTs, No. (%)		Univariable		Multivariable	
	Discontinued Because of Poor Recruitment (n = 90)	Completed (n = 526)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Planned target sample size, median (IQR)	180 (80-320)[b]	368 (154-800)[b]	0.95 (0.91-0.99)[b,c]	.01	0.96 (0.92-1.00)[b,c]	.04
Placebo/no active control (vs active-control intervention)	53 (58.9)	321 (61.1)	0.89 (0.56-1.41	.63	0.81 (0.50-1.31)	.39
Single-center status (vs multicenter)	19 (21.1)	53 (10.1)	2.41 (1.35-4.32)	.003	0.66 (0.32-1.38)	.27
Crossover design (vs parallel)	8 (8.9)	21 (4.0)	2.37 (1.01-5.53)	.046	2.00 (0.75-5.33)	.16
Reported methodological/logistical support (vs not reported)	27 (30.0)	245 (46.7)	0.50 (0.31-0.81)	.005	0.62 (0.37-1.06)	.08
Reported recruitment projection (vs not reported)	12 (13.3)	40 (7.6)	1.71 (0.84-3.47)	.14	1.04 (0.50-2.22)	.90
Industry sponsor (vs investigator)	34 (37.8)	371 (70.5)	0.25 (0.16-0.40)	<.001	0.25 (0.15-0.43)	<.001

Abbreviation: IQR, interquartile range.

[a] Complete-case multilevel logistic regression analysis of patient RCTs (research ethics committees as random intercept); RCTs involving healthy volunteers (n = 123), RCTs discontinued for reasons other than poor recruitment (n = 149), RCTs with unclear completion status (n = 70), pilot RCTs (n = 51), and cluster RCTs (n = 8) were excluded, for a total of 616 trials. In addition, we excluded 5 RCTs with missing values for target sample size (footnote "b"). A sensitivity analysis with target sample size imputed through multiple imputation including these 5 RCTs showed similar results (eTable 3 in Supplement).

[b] Trials with missing values for target sample size were excluded.

[c] In increments of 100.

Table 4. Factors Associated With Nonpublication of Randomized Clinical Trials (RCTs)[a]

Characteristics	RCTs, No. (%)		Univariable		Multivariable	
	Not Published (n=451)	Published (n=566)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Planned target sample size, median (IQR)	120 (40-330)[b]	303 (100-745)[b]	0.92 (0.89-0.94)[c]	<.001	0.95 (0.92-0.97)[c]	<.001
Multicenter status (vs single center)	280 (62.4)	470 (83.0)	0.33 (0.25-0.44)	<.001	0.50 (0.32-0.76)	.001
Industry sponsor (vs investigator)	279 (61.9)	358 (63.3)	0.94 (0.73-1.22)	.65	1.68 (1.20-2.34)	.002
Discontinued RCT (vs completed RCT)	140 (37.6)[d]	114 (20.1)[d]	2.41 (1.80-3.24)	<.001	3.19 (2.29-4.43)	<.001
RCT with patients (vs healthy volunteers)	364 (80.7)	530 (93.6)	0.27 (0.17-0.41)	<.001	0.36 (0.20-0.63)	<.001

Abbreviation: IQR, interquartile range.

[a] Complete-case multilevel logistic regression analysis of RCTs involving patients and RCTs with healthy volunteers (research ethics committees as random intercept); we excluded 12 RCTs with missing values for planned target sample size (footnote "b") and 81 RCTs with unclear completion status (footnote "d"), for a total of 924 RCTs. A sensitivity analysis including these 93 RCTs (total n = 1017) with imputations for unclear completion status and target sample sizes imputed through multiple imputation showed similar results (eTable 3 in Supplement).

[b] Trials with missing values for sample size were excluded.

[c] In increments of 100.

[d] Trials with unclear completion status were excluded.