Akademickie badania kliniczne

Zbigniew Gaciong

Katedra i Klinika Chorób Wewnętrznych, Nadciśnienia Tętniczego i Angiologii

Warszawski Uniwersytet Medyczny

Warszawski Uniwersytet Medyczny, 20 maja 2014

Pierwsze opublikowane badanie kliniczne z randomizacją

Hipoteza: ...Obawiam się, by mój pan, król, który przydzielił wam pożywienia i napoje, nie ujrzał, że wasze twarze są chudsze niż młodzieńców w waszym wieku ...

Materiał i Metody: „Poddaj sługi twoje dziesięciodniowej próbie: niech nam dadzą jarzyny do jedzenia i wodę do picia. Wtedy zobaczysz jak my wyglądamy a jak wyglądają młodzieńcy jedzący potrawy królewskie.”

Wyniki i Wnioski: Po upływie dziesięciu dni wygląd ich był lepszy i zdrowszy niż innych młodzieńców. Którzy spożywali potrawy królewskie. Strażnik zabierał więc ich potrawy i wino do picia, a podawał jarzyny.

Księga Daniela, Księgi Prorockie, Stary Testament

(w przekładzie Zespołu Biblistów Polskich)

Szukaj

- **Start**
  - Strona główna
- **Studia podyplomowe**
  - Metodologia Badań Klinicznych
  - Zarządzanie Zasobami Ludzkimi w Organizacjach Ochrony Zdrowia
  - Zarządzanie Projektami Medycznymi
  - Zarządzanie Spółką Prawa Handlowego Ochrony Zdrowia
  - Prowadzenie Działalności

Metodologia Badań Klinicznych

Informacje dla kandydatów

Studia przeznaczone są dla osób będących pracownikami jednostek klinicznych i naukowych lub prowadzących badania na zlecenie.
W pierwszej kolejności zapraszamy osoby, które ukończyły studia z zakresu nauk biomedycznych i (lub) posiadają minimum roczne doświadczenie w badaniach klinicznych.
Zapraszamy również pracowników lub kandydatów na pracowników działów medycznych firm farmaceutycznych lub firm o typie CRO i SMO.

Zasady rekrutacji

Rekrutacja na V* edycję studiów - OTWARTA

- O przyjęciu na studia decyduje wynik **postępowania kwalifikacyjnego** prowadzonego na podstawie złożonych dokumentów.
- **Limit miejsc**: 50

Osoby zainteresowane udziałem w studiach proszone są o przesyłanie do Dziekanatu Centrum

Cooperative European Medicines Development Course

Estonia, Tartu

Hungary, Budapest
(Coordinating center: Semmelweis University)

Lithuania, Kaunas

Poland, Warsaw

Portugal, Lisbon

Romania, Targu Mures

Serbia, Belgrade

Slovakia, Bratislava

Slovenia, Ljubljana

Turkey, Ankara

Base Course

Covering all topics of the syllabus

1. Discovery of Medicines

2. Development of Medicines: Planning

3. Non-Clinical Testing

4. Pharma-ceutical development

5. Exploratory development

6. Confirmatory development

7. Clinical trials

8. Ethics legal issues

9. Data management Statistics

10. Regulatory affairs

11. Drug Safety

12. Information, promotion

13. Economics of Healthcare

14. Therapeutics

Base course (6 base modules, 30 ECTS)

1. Introduction. Drug discovery
2. Non-clinical drug development
3. Early clinical drug development
4. Confirmatory clinical drug trials
5. Drug regulation and pharmacovigilance
6. Healthcare, marketplace, economics of healthcare

Akademickie badania kliniczne

- Non-commercial
- Investigator-driven
- Investigator-initiated

Akademickie badania kliniczne

- Rozwiązanie problemów „nieopłacalnych” dla przemysłu
- Mniejsze koszty
- Większa wiarygodność wyników

Typy badań klinicznych

- Opis przypadku
- Opis serii przypadków
- Badanie obserwacyjne vs eksperymentalne
  - z grupą kontrolną (case-control)
  - kohortowe (cohort)
- Prospektywne vs retrospektywne
- Kontrolowane, prospektywne (RCT, randomized controlled trial)
  - z podwójnym zamaskowaniem (double-blind)
  - PROBE (prospective randomized open-label blinded end-point)
- Meta-analizy
- Rejestry

Typy akademickich badań klinicznych

- **Opis przypadku**
- **Opis serii przypadków**
- **Badanie obserwacyjne** vs eksperymentalne
  - z grupą kontrolną (case-control)
  - kohortowe (cohort)
- Prospektywne vs **retrospektywne**
- Kontrolowane, prospektywne (RCT, randomized controlled trial)
  - z podwójnym zamaskowaniem (double-blind)
  - PROBE (prospective randomized open-label blinded end-point)
- Meta-analizy
- **Rejestry**

Akademickie badania kliniczne – podstawowe odrębności

Badanie kliniczne (*clinical trial*)

Wielo-ośrodkowe badanie kliniczne (*Multi-center clinical trial*) - rzadko

Badanie nie-interwencyjne (*Non-interventional clinical trial*) - najczęściej

Badany produkt leczniczy (*Investigational medicinal product*)

- zwykle nowe wskazania, badania mechanizmu

Sponsor (*Sponsor*) – Grant

Badacz (*Investigator*) – autor protokołu

Broszura badacza (*Investigators brochure*)

Protokół (p*rotocol*)

Świadoma zgoda na udział w badaniu (*Informed consent)*

Komisja etyczna (E*thics committee)*

Inspekcja (I*nspection)*

Zdarzenie niepożądane (*Adverse event)*

Typy badań klinicznych w najczęściej cytowanych publikacjach (1994-2003)

Rodzaj	Liczba
Kontrolowane badanie kliniczne (RCT)	77
Meta-analiza	5
Wytyczne/standardy (guidellines)	6
Klasyfikacja/definicja choroby	7
Opisowa statystyka danych epidemiologicznych dotyczących częstych chorób	20
Badania kohortowe nad czynnikami ryzyka	6
Obserwacje dotyczące działań niepożądanych	1
Badania niekontrolowane nad Eksperymentalne metody terapeutyczne	12
Nowe metody terapii	9
Ekspresja genów/proteonomika	9
Genetyczne uwarunkowanie chorób	14
Badania doświadczalne z materiałem pochodzącym od ludzi	45
Badania doświadczalne z materiałem niepochodzącym od ludzi	33
Prace poglądowe bez danych oryginalnych	44
Artykuł redakcyjny na temat EBM	1
Łącznie	289

BMJ

Patsopoulos, N. A et al. BMJ 2006;332:1061-1064

Akademickie badania kliniczne
Podstawowa charakterystyka

- Większość o charakterze badań epidemiologicznych
- Małe grupy chorych
- Brak odpowiedniego opracowania statystycznego
- „Ukryty” sponsoring
- „Niezauważana” konieczność zgłaszania potencjalnego konfliktu interesu

Akademickie badania kliniczne - problemy

- Regulacja

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Article 2c

'Non-interventional trial': a study where the medicinal product(s) is (are) **prescribed in the usual manner** in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. **No additional diagnostic or monitoring procedures shall be applied to the patients** and epidemiological methods shall be used for the analysis of collected data

COMMISSION DIRECTIVE 2005/28/EC

of 8 April 2005

laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

(Text with EEA relevance)

(11)

Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned. Directive 2001/20/EC recognises the specificity of these non-commercial clinical trials. In particular, when trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indication, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, should be taken into consideration. However, it could also be necessary, due to the specific conditions under which noncommercial trials are conducted, that Member States foresee **specific modalities to be applied to these trials** not only when conducted with authorised medicinal products and on patients with the same characteristics, in order to comply with the principles imposed by this Directive, in particular as far as the manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the noncommercial research is conducted by public researchers and the places where this research takes place, make the **application of certain of the details of good clinical practice unnecessary or guaranteed by other means**. Member States will ensure in these cases, when providing for specific modalities, that the objectives of the protection of the rights of patients who participate in the trial, as well as, in general, the correct application of the good clinical practice principles, are achieved. **The Commission will prepare a draft** with guidance in this respect.

COMMISSION DIRECTIVE 2005/28/EC

of 8 April 2005

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DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Article 2 (c)

Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned. The Directive should therefore take account of the **special position of trials** whose planning does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directives 75/319/EEC and 91/356/EEC, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation. Labelling of the investigational medicinal products intended for trials of this nature should be subject to **simplified provisions** laid down in the good manufacturing practice guidelines on investigational products and in Directive 91/356/EEC.

MAYBE YOU CAN HELP SAVE EUROPEAN RESEARCH

Why did the European Union decide to stop cancer research?

English | Français | Español | Deutsch | Italiano

Dear MEPS,

"Why did the European Union decide to stop cancer research?"

This is the question which European Parliamentarians, Commissioners and officials will be asked by their constituents in May 2004. On that date the European Commission Directive (2001\20\EC) (download PDF) on clinical trials comes into force. This directive places such high administrative expenses in the way of patient-focused research, that it will effectively end all clinical research except for those trials which are commercially-inspired, and drug company-sponsored. The bulk of cancer research trials are currently conducted, not by the industry, but on a voluntary basis by cancer specialists and charities, who simply do not have the resources to meet these new requirements. Thus, trials which are vital to the best interests of patients, but are of no interest to the pharmaceutical industry, either because they involve generic or widely available drugs, or (as is the case in trials of screening, radiotherapy and surgery), no drugs at all, will be nearly impossible to conduct. Investigations of new treatments for those rare fatal cancers which affect children may stop altogether.

If this directive had been introduced forty years ago, many of the most critical advances in cancer treatment would not have been made. Women with breast cancer would still have to lose their breasts, and patients with throat cancer their voice boxes. Childhood leukemia would still be a death sentence rather than a great success story of cancer research.

The Directive represents a solution which is not needed to a problem which does not exist.

It is no easier for organizations than it is for individuals to admit that they have made a mistake. The EU had made one here, and public pressure will force its correction. The question is whether it will be corrected now before it costs lives, or later, after it has.

We respectfully urge the European Parliament to repeal this directive before it comes into force.

PLEASE CHANGE DIRECTIVE 2001\20\EC - BEFORE IT'S TOO LATE

Yours Sincerely

Please add your signature electronically to this letter.

Organisations that support this initiative:

EORTC

SIOG

GBG GERMAN BREAST GROUP

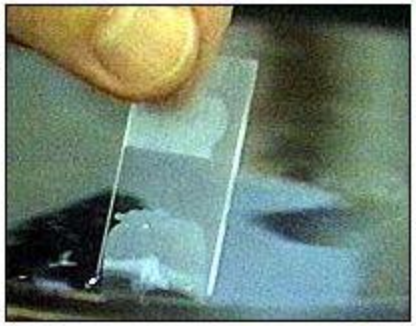
GEICAM

BNGO Berufsverband Niedergelassener Gynäkologischer Onkologen in Deutschland e.V.

Updated: Tuesday, 20 January, 2004, 09:53 GMT

d tape poses threat to research

lical experts are warning inst a European Directive ch they claim will ously jeopardise earch in areas such as cer.



Research costs may go up

aim of the new law - ch member states are due dopt in May - is to improve ty by standardising clinical s.

researchers say increased red tape will send costs of vital cal trials soaring.

e than 2,000 researchers have signed a petition against measures.

y are concerned that the ctive was designed only big pharmaceutical panies in mind.

they warn that medical rities - who often work on oestring - may not be able ope with overbearing eaucratic demands.

> **Our problem with this directive is simply that the bureaucracy of a lot of elements within the directive is going to outstrip any potential protection for patients.**
>
> Dr Richard Sullivan

consultation

ichard Sullivan, from Cancer Research UK, said the

SEE ALSO:
- Cancer research 'under threat' 05 Jul 03 | Health
- Row over medical research claim 30 Oct 03 | Health

RELATED INTERNET LINKS:
- Cancer Research UK
- European Union
- Medical Research Council

The BBC is not responsible for the content of external internet sites

TOP HEALTH STORIES NOW
- Sick baby's family thanks judge
- Drug trial families given apology
- Spousal death 'not so upsetting'
- Bird flu 'causes first dog death'

RSS | What is RSS?

BNHO

Website provided by:

combinedmedia

Please sign to show your support:

Title: Prof	First Name: Zbigniew	Surname: Gaciong	
Position: Dean	Email: zgaciong@hotmail.com (If you would like to be kept updated on the progress of this initiative)		
Institution: dical University of Warsaw	Signed on behalf of (if applicable)		
Location: Poland	Submit		

SOME EARLY SIGNATORIES OF THE PETITION

Prof.	**John**	**Crown**	St. Vincent's University Hospital	Chairman Breast Committee, Irish Clinical Oncology Research Group	**Ireland**
Dr.	**Brian**	**Moulton**	Chief Executive Officer Irish Clinical Oncology Research Group	Member of EU Steering Group for Cancer Research Management, ECRM	**Ireland**
Prof.	**Martine**	**Piccart**	On behalf of Institut Jules Bordet and all Belgian Cancer Researchers	Chairperson, Breast International Group (BIG)	**Belgium**
Dr.	**Carolyn**	**Straehle**	Managing Director Breast International		**Belgium**

Wpływ Dyrektywy 2001/20/EC na badania kliniczne w EU

- 60% sponsorowane przez przemysł
- 24% badania wieloośrodkowe, obejmujące 67% wszystkich uczestników zarejestrowanych badań

- Spadek liczby aplikacji o 25% pomiędzy rokiem 2007 a 2011
- Wzrost kosztów dla CRO i regulatora (zwiększenie liczby personelu o 107%)
- Dla podmiotów niekomercyjnych wzrost kosztów o 98%
- Zwiększenie kosztów ubezpieczenia o 800%
- Wydłużenie czasu do rozpoczęcia badania o 90% do 152 dni

Niekorzystny wpływ Dyrektywy Europejskiej na akademickie badania kliniczne

- Spadek liczby badań klinicznych o 63%
- Zmniejszenie liczby włączonych chorych o 33%
- Koszty prowadzenia badań wzrosły o 85%
- Opóźnienie okresu rozpoczęcia badań o 5 miesięcy
- Znaczne zwiększenie obciążenia pracą Komisji Etycznych

The European Organization for Research and Treatment of Cancer

European Cancer Conference, Paryż, listopad 2005

Commentary: Is society losing control of the medical research agenda?

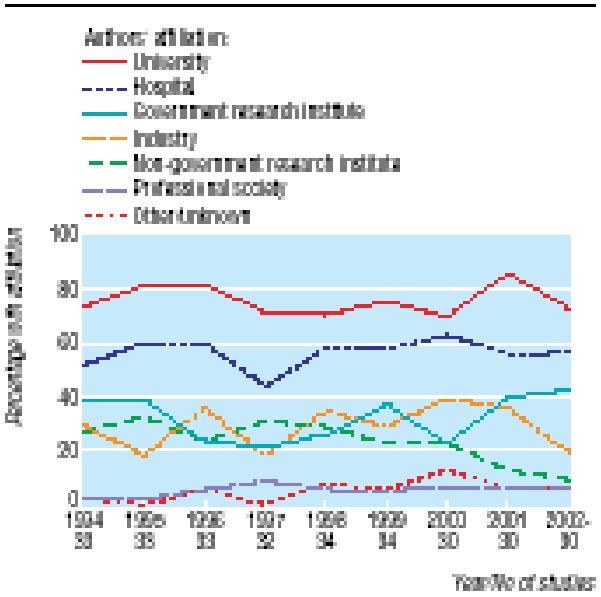
Brendan Delaney

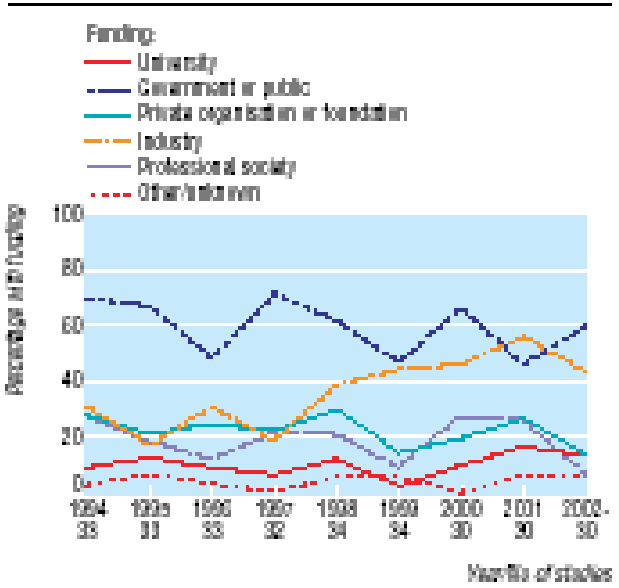
- Od 1994 roku zaznacza się wzrost liczby badań finansowanych przez przemysł
- Najczęściej cytowane prace co raz rzadziej posiadaja autorów afiliowanych w uczelniach
- Większość znaczących dla praktyki medycznej badań finansuje przemysł

BMJ

BMJ 2006;332:1065-1066

Malejący udział badań „akademickich” wśród znaczących badań klinicznych





Patsopoulos NA.BMJ online, 17 March 2006

EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

DRAFT

Draft guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice

Non-commercial Clinical Trials

- The sponsor should be a university, a hospital, a public scientific organisation, a non profit institution, a patient organisation or a researcher;
- The ownership of the data of these trials should belong to the sponsor listed in the first bullet point;
- No agreements between the sponsor and third parties allowing them to use the data for regulatory or marketing purposes should be in place; and
- The design, conduct, recording and reporting of the clinical trial should be under the control of the sponsor.
- The studies should not be part of the development programme for a marketing authorisation of a medicinal product.

EUROPEAN COMMISSION

Brussels, 17.7.2012
SWD(2012) 201 final

COMMISSION STAFF WORKING DOCUMENT

EXECUTIVE SUMMARY OF THE IMPACT ASSESSMENT REPORT ON THE REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

Accompanying the document

Proposal for a Regulation of the European Parliament and of the Council

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

{COM(2012) 369 final}
{SWD(2012) 200 final}

Proposal for an EU Regulation on Clinical Trials

A joint statement from non-commercial and commercial organisations

We welcome the proposal for a Clini… an Commission. The Regulation appears … his will give clinicians and researchers a b… efit patients across Europe, while maint… in European clinical research. The harmo… lication process for starting trials should … n Europe.

This statement outline… ities on where the Regulation will improv… ld be improved to further support clinica… of the Regulation continue to be debated… nd proportionate approaches to certain a…

„Low-intervention clinical trial”

(all of conditions fullfiled)

- the investigational medicinal products are authorised; according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the
- marketing authorisation or their use is a standard treatment in any of the Member States concerned;
- the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Do czy badania retrospektywne wykonywane w oparciu o analizę dokumentacji chorych wymagają...

- ... Opinii komisji etycznej?
- TAK, jeśli mają cel naukowy

- ... Zgody badanego?
  - NIE ZAWSZE, jeśli KE nie widzi konieczności uzyskania

Badania retrospektywne wykonywane w oparciu o analizę dokumentacji wymaga zgody pacjenta, jeśli:

- Wykorzystuje jego dane osobowe
- Wykorzystuje zgromadzony materiał biologiczny

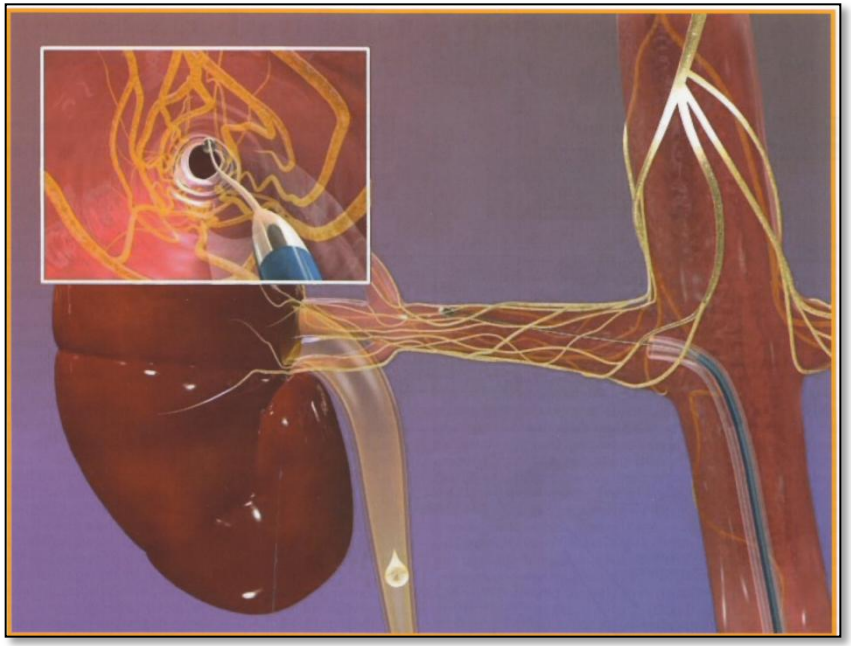
Akademickie badania kliniczne - problemy

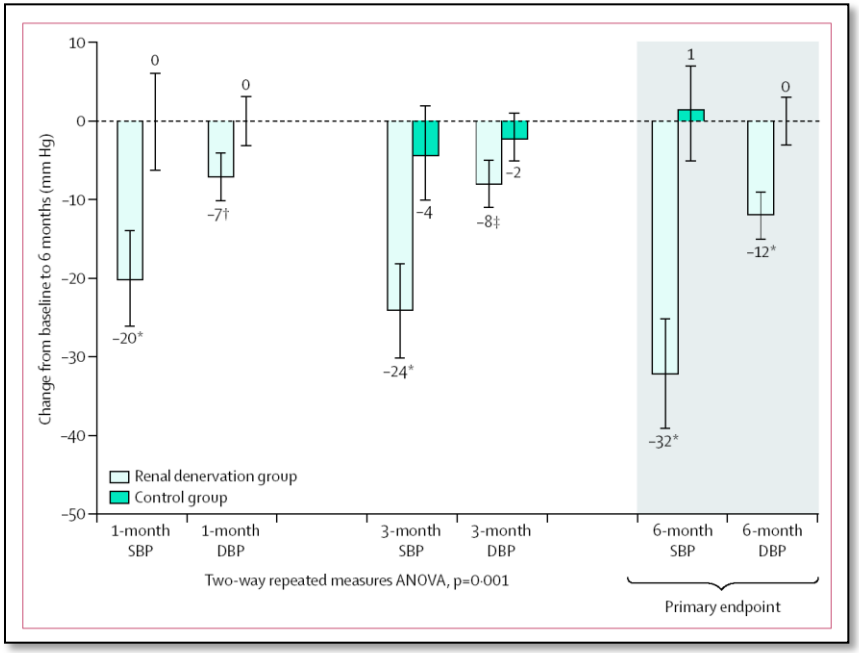
- Wykonawcy

Akademickie badania kliniczne
Podstawowe problemy organizatorów

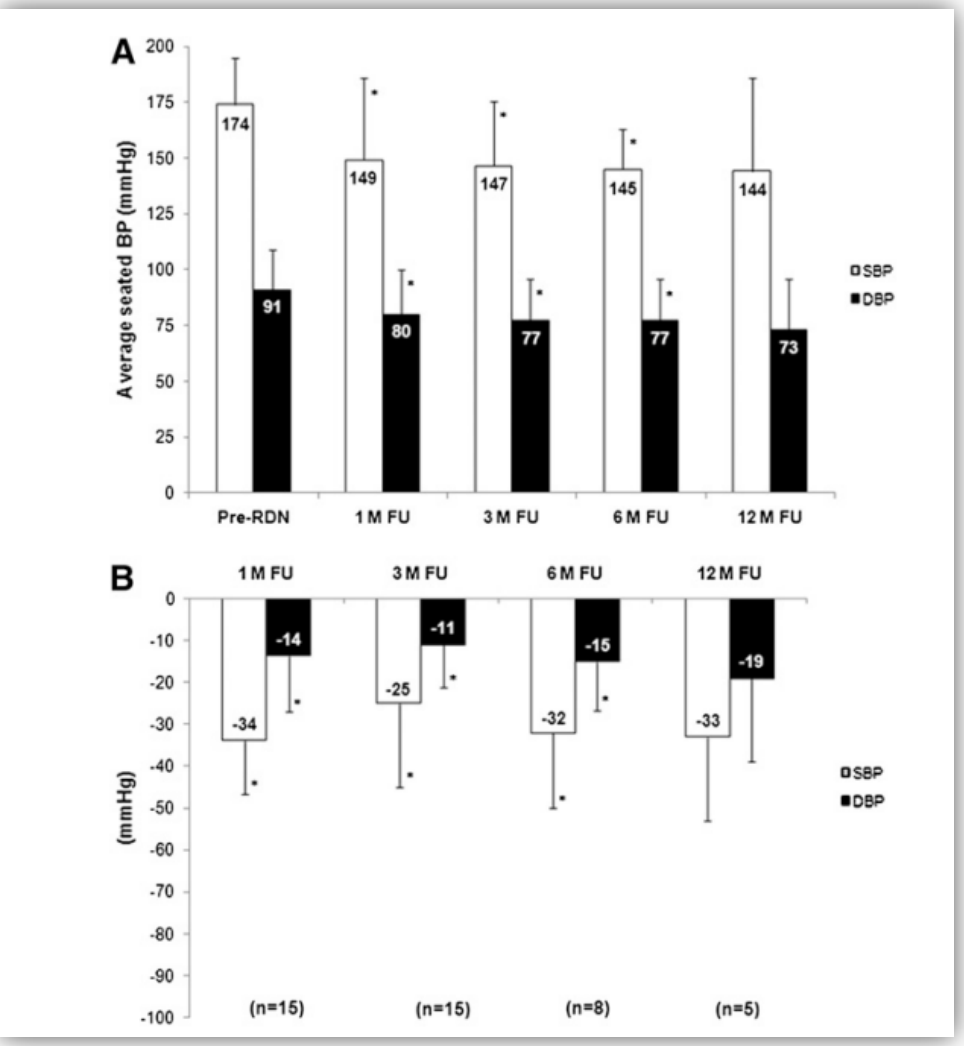
- Nieznajomość ICH GCP przez badaczy
- Zbyt małe możliwości KE do rozpatrywania wniosków i analizy dokumentacji
- Brak odpowiedniego ubezpieczenia badania
- Negatywna postawa wobec badań z placebo

Renal denervation: SIMPLICITY HTN Trials





Denerwacja powoduje kontrolę ciśnienia tętniczego u pacjentów z nadciśnieniem tętniczym i niewydolnością nerek



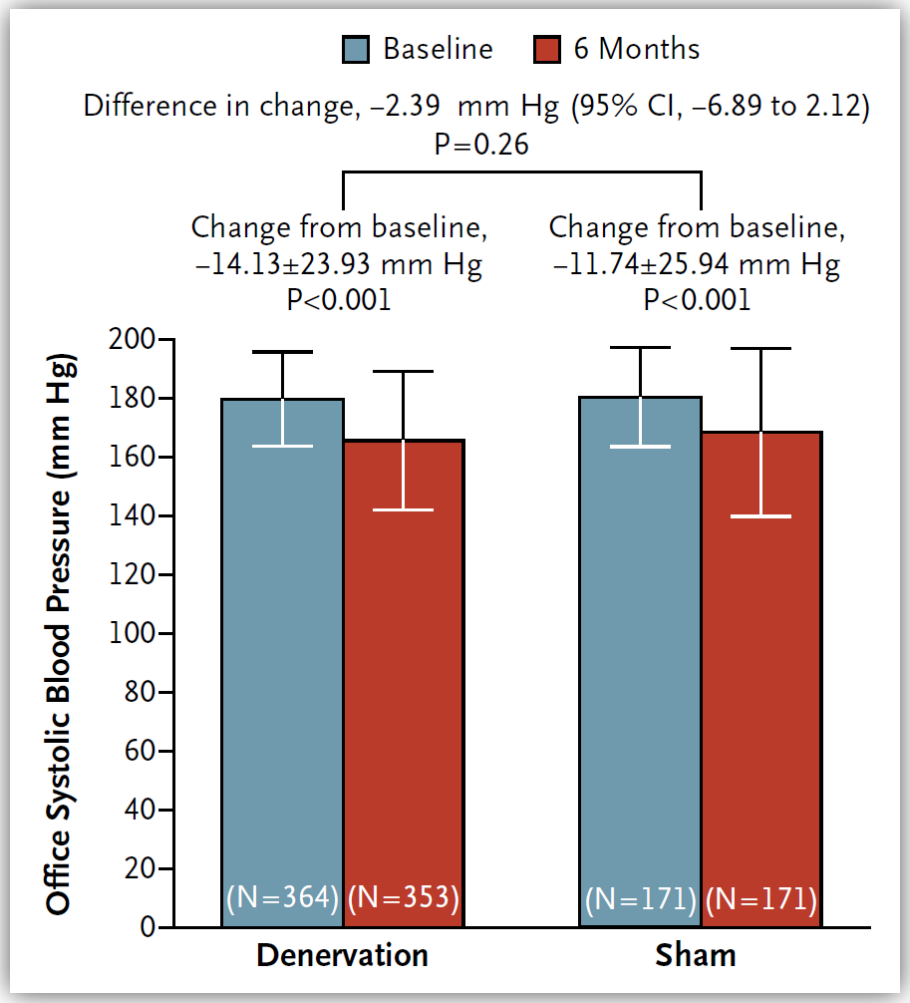
Dagmara Hering et al. Renal Denervation in Moderate to Severe CKD. J Am Soc Nephrol 23: 1250–1257, 2012

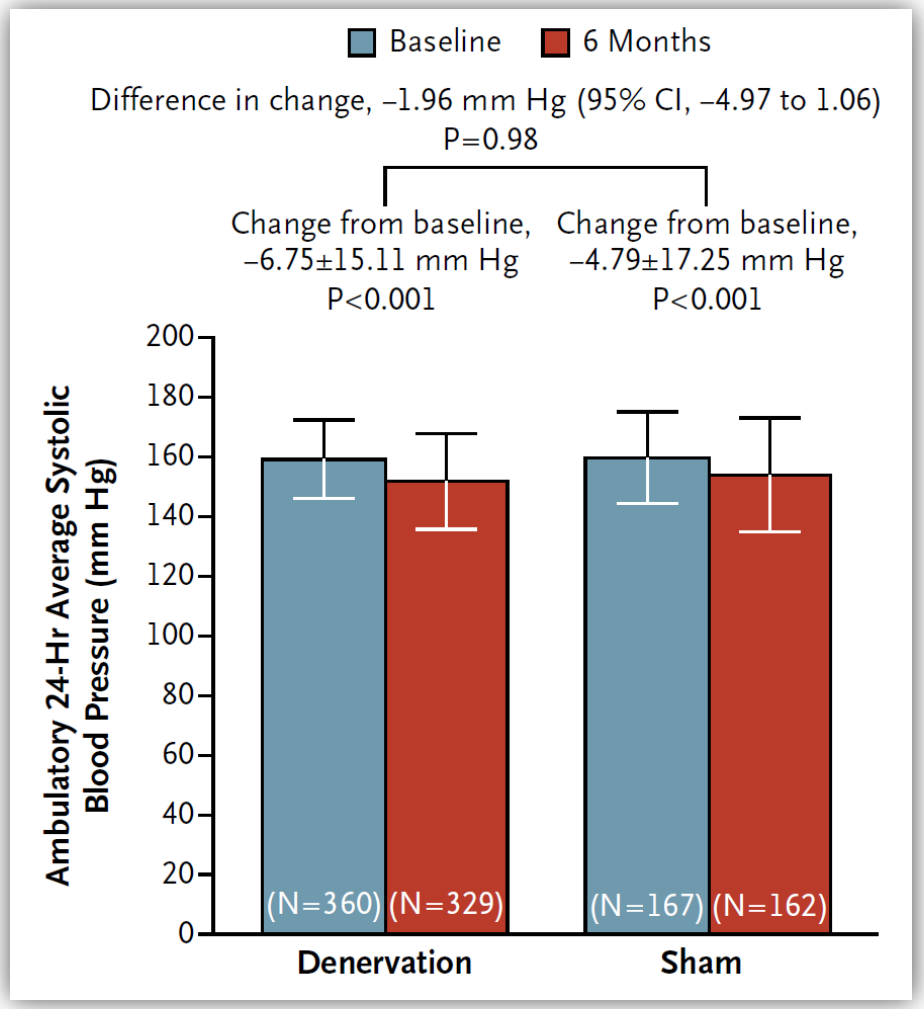
The Joint UK Societies' Consensus Statement on Renal Denervation for Resistant Hypertension.

Steering Group: Mark Caulfield[1] (Chair), Mark de Belder[2], Trevor Cleveland[3], David Collier[1], John Deanfield[4], Huon Gray[5], Charles Knight[5], Melvin Lobo[1], Matthew Matson[3], Jon Moss[3], Neil Poulter[1], Iain Simpson[5], Charles Tomson[6], Bryan Williams[1].

On behalf of the British Hypertension Society[1], the British Cardiovascular Intervention Society[2], the British Society for Interventional Radiology[3], National Institute for Clinical Outcomes Research[4], the British Cardiovascular Society[5], and the Renal Association[6].

SIMPLICITY HTN 3: Brak znaczącego wpływu denerwacji na kontrolę ciśnienia tętniczego





A Controlled Trial of Renal Denervation for Resistant Hypertension. DOI: 10.1056/NEJMoa1402670

The Joint UK Societies Working Group on Renal Denervation.
Initial response to the Medtronic Symplicity HTN3 announcement.

Mark Caulfield[1] (Chair), Mark de Belder[2], Trevor Cleveland[3], David Collier[1], Indranil Das Gupta, John Deanfield[4], Huon Gray[5], Charles Knight[5], Melvin Lobo[1], Matthew Matson[3], Jon Moss[3], Neil Poulter[1], Iain Simpson[5], Bryan Williams[1].

On behalf of the British Hypertension Society[1], the British Cardiovascular Intervention Society[2], the British Society for Interventional Radiology[3], National Institute for Clinical Outcomes Research[4], the British Cardiovascular Society[5], and the Renal Association[6].

- While we await the data from Symplicity HTN3, we recommend a temporary moratorium on renal denervation procedures for all cases as part of routine care in the NHS and private practice in the UK.

Akademickie badania kliniczne - problemy

- Finansowanie

Akademickie badania kliniczne
Źródła finansowania

- Narodowe Centrum Badań i Rozwoju (STRATEGMED, INNOMED, PBS)
- Narodowe Centrum Nauki (?)
- Ministerstwo Nauki i Szkolnictwa Wyższego
  - działalność statutowa
  - Projekty („Wybitny badacz”, „Diamentowy Grant”, Iuventus Plus, …
- Ministerstwo Zdrowia (programy naukowe)
- Fundacja Na Rzecz Nauki Polskiej
- Fundacja Na Rzecz Wspierania Polskiej Farmacji i Medycyny
- Przemysł Farmaceutyczny (*independent grants, extramural projects)*
- Inne (?)

Presence: last 15 years - cardiology

„What I called the **clinical trial – guideline – education process** is having profound effect on cardiology research and practice – effects almost as significant, as the invention of the stethoscope in France in 1816 and the electrocardiograph in Holland in 1902”

W. Bruce Fye J Am Coll Cardiol 2003; 41 (8): 1237

Specyfika akademickich badań klinicznych
Podsumowanie

- Zwykle jedność sponsora, badacza i instytucji opiniującej
- Zwykle o charakterze badań epidemiologicznych
- Najczęściej celem jest poznanie mechanizmu choroby
- Brak jednoznacznej regulacji prawnej
- Niedostateczna znajomość zasad GCP
- Brak właściwego ubezpieczenia
- Negatywne nastawienie mediów

Badanie Kliniczne

- stosuje substancje albo mieszaninę substancji, którym nadano postać farmaceutyczna substancji czynnej lub placebo
- wymieniona substancja jest stosowana jako produkt badany lub referencyjny
- produkt dopuszczony do obrotu ale stosowany lub przygotowany w sposób odmienny od postaci dopuszczonej do obrotu
- produkt dopuszczony do obrotu ale stosowany we wskazaniu nieobjętym pozwoleniem
- produkt dopuszczony do obrotu ale stosowany w celu uzyskania dodatkowych informacji