AIFA
AGENZIA ITALIANA DEL FARMACO

Nuovi strumenti regolatori: revisioni sistematiche, coinvolgimento dei pazienti e comunicazione sanitaria – un continuum più coerente?

Il contributo di Alessandro Liberati e Cochrane Italia all'approvazione di nuovi farmaci e vaccini

Towards new tools for regulators: systematic reviews, patient engagement and health communication – a more consistent continuum?

The contribution of Alessandro Liberati and Cochrane Italy to the approval of new medicines and vaccines

GIOVEDÌ 27 GENNAIO 2022 · ORE 15:30 - 17:00

THURSDAY 27 JANUARY 2022 · 15:30 - 17:00 (CET)

1994: Cochrane Collaboration, EBM, and Publication Bias

BMJ, January 2007
15 medical milestones during last century

- Antibiotics
- Imaging
- Tissue culture
- Anaesthesia
- Chlorpromazine
- Sanitation
- Germ theory
- Evidence based medicine
- Vaccines
- Contraceptive pill
- Computer technology
- Oral rehydration therapy
- Monoclonal antibody technology
- Smoking risks
- Structure of DNA

Increasing, not dictating, choice

Kay Dickersin, Sharon E Straus, Lisa A Bero

The systematic synthesis of evidence is the foundation of all medical discoveries and of good clinical practice

Logo of the journal *Evidence-Based Medicine*

Evidence based medicine is healthcare practice that is based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients' values and circumstances. It is curious, even shocking, that the adjective "evidence based" is needed. The public must wonder on what basis medical decisions are made otherwise. Is it intuition? Magic? The public must also wonder what happens to the research evidence in which they have invested—either directly through taxes or indirectly through buying drugs and other medical products—if it is not guiding clinical practice.

How could something so intuitively obvious to lay people not be similarly viewed by clinicians? And how could this medical milestone be so misunderstood by some? Critics of evidence based medicine worry that it dictates a single "right" way to practise, despite differences among patients; that some self appointed group of "experts" will declare only one type of study to be useful; or that healthcare decisions will be made solely on the basis of costs and cost savings.

Giving a name to evidence based medicine and, now, awarding it milestone status could help everyone to realise that it is about making decisions that are based on the best available evidence, not dictating what clinicians do.

Establishing a modern milestone

The term "evidence based medicine" was coined in 1991 by a group at McMaster University, Ontario. It arose from a confluence of events and changes in our culture. These included a growing recognition that:

- The systematic synthesis of all reliable information on a topic has greater value than traditional reviews
- Bias can explain results in many individual studies, and randomised clinical trials are now recognised as the study design that is best suited to avoiding bias in questions of intervention effectiveness, although other types of study may be better for other types of questions
- Tragedy can result from paying attention to poor quality evidence instead of good quality evidence
- Clinicians need information, and they don't get enough from the sources they typically use
- The medical literature is growing exponentially, and there is not enough time in the day to read even the good stuff, and
- Undesirable gaps and variation in practice exist.

> It is curious, even shocking, that the adjective "evidence based" is needed

Imagine a world without evidence based medicine. Most women with early breast cancer would still be undergoing mastectomy instead of lumpectomy and radiation. Now they can choose.

Many babies born prematurely would still be dying from respiratory distress syndrome, not having the advantage of a mother who took corticosteroids or of being given surfactant themselves.

Pregnant women in Boston might still be taking diethylstilbestrol to prevent miscarriage, on the enthusiastic recommendation of well respected local experts, with the result that many of their children would be developing reproductive abnormalities and cancer.

A boy with asthma might have his treatment changed every six weeks as new drug samples are dropped off at his doctor's surgery. The choice of drug to help prevent a second fracture in an elderly woman might be made on the basis of television advertisements.

Finally, without evidence based medicine, precious health resources might have been spent unnecessarily. In the United States, research into preventing and treating AIDS has cost $30bn (£16bn; 23bn) since 1981. Had the research results not been applied to practice, more than 50% of hospital beds in the US would be filled with AIDS patients, at a cost of $1.4 trillion. Similarly, without the application of cardiovascular research from 1982 to the present, the cost of treating these patients would be 35% higher.

Making the evidence accessible

What is the future for evidence based medicine? The biggest challenge will be getting all clinicians, consumers, policy makers, and other stakeholders on board. We need to help the naysayers to understand what evidence based medicine is and what it isn't. It seems obvious to say that we also need to seek evidence that it is useful. The results of evidence based medicine often clash with the agenda of special interest groups. The challenges created by rich and powerful manufacturers of drugs and devices cannot be overemphasised. Not to be left behind, the industry is developing its own systematic reviews and making them public.

We need to alert clinicians and patients to studies showing that reviews sponsored by the industry almost always favour the sponsor's product, whereas those that aren't sponsored by such companies do not. We also need to provide patients and the general public with the tools to enable them to understand and evaluate systematic reviews. Finally, it is not enough to create high quality, evidence based resources: we need to ensure global access to them.

The question has moved beyond "Why is evidence based medicine important?" to "Why is it not already a reality?" and "How can we all work together to make it a reality, quickly?" Evidence based medicine is one of our most important medical milestones because, without it, the other 14 of the *BMJ*'s milestones would not have been implemented.

Kay Dickersin, professor
Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore
Sharon E Straus, associate professor
Department of Medicine, University of Calgary, Calgary, Alberta
Lisa A Bero, professor
Department of Clinical Pharmacy and Institute for Health Policy Studies, University of California, San Francisco

Today three main topics only:

- Role of systematic reviews (or the risks of publications bias)
- Patients/citizens involvement (or information vs persuasion)
- Estimating/communicating risks and benefits

Other topics for another meeting:

- EBM evolution
- RCTs when and how and research ethics
- Independent research
- Guidelines making and implementation

1. Examples of publication bias

Studies with apparently conflicting results selectively reported

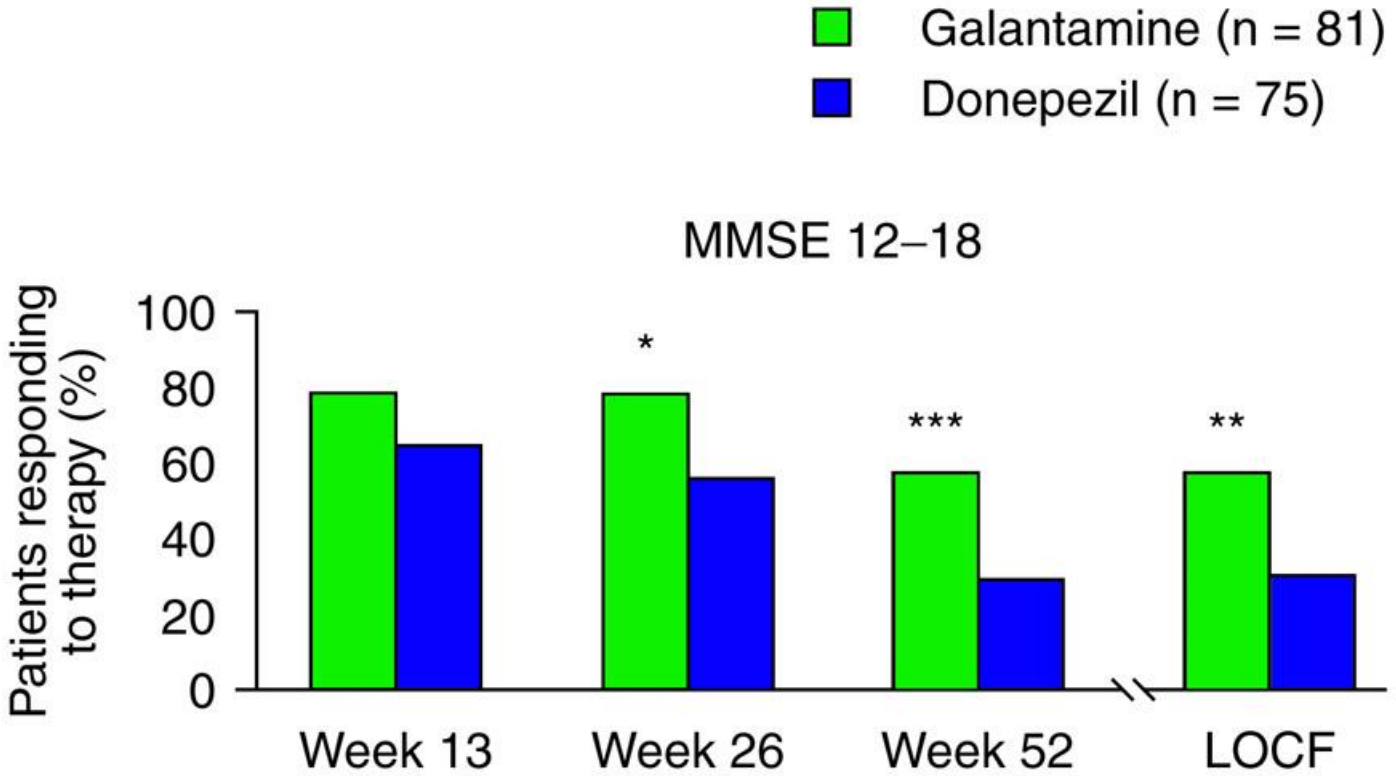
A Long-Term Comparison of Galantamine and Donepezil in the Treatment of Alzheimer's Disease

Gordon Wilcock,[1] Ian Howe,[2] Hilary Coles,[3] Sean Lilienfeld,[4] Luc Truyen,[5] Young Zhu,[5] Roger Bullock[6] and Members of the GAL-GBR-2 Study Group

1 Department of Care of the Elderly, University of Bristol, Frenchay Hospital, Bristol, UK
2 Shire Pharmaceuticals, Ltd., Chineham, Basingstoke, Hampshire, UK
3 Janssen-Cilag UK, Saunderton, High Wycombe, Buckinghamshire, UK
4 Janssen Pharmaceutica Products, L.P., Titusville, New Jersey, USA
5 Johnson & Johnson Pharmaceutical Research & Development, LLC, Titusville, New Jersey, USA
6 Department of Old Age Psychiatry, Kingshill Research Centre, Victoria Hospital, Swindon, UK

Study funded by Galantamine manufacturer

Wilcock G et al. Drugs Aging 2003;20:777-89



Proportion of galantamine and donepezil recipients responding to therapy (improvement or no change in MMSE score vs baseline); results in the total population and subgroup with baseline MMSE scores of 12–18. **LOCF** = last observation carried forward; **MMSE** = Mini-Mental State Examination; * $p \leq 0.01$, ** $p \leq 0.005$, *** $p < 0.001$ vs donepezil.

Wilcock G et al. Drugs Aging 2003;20:777-89

A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease

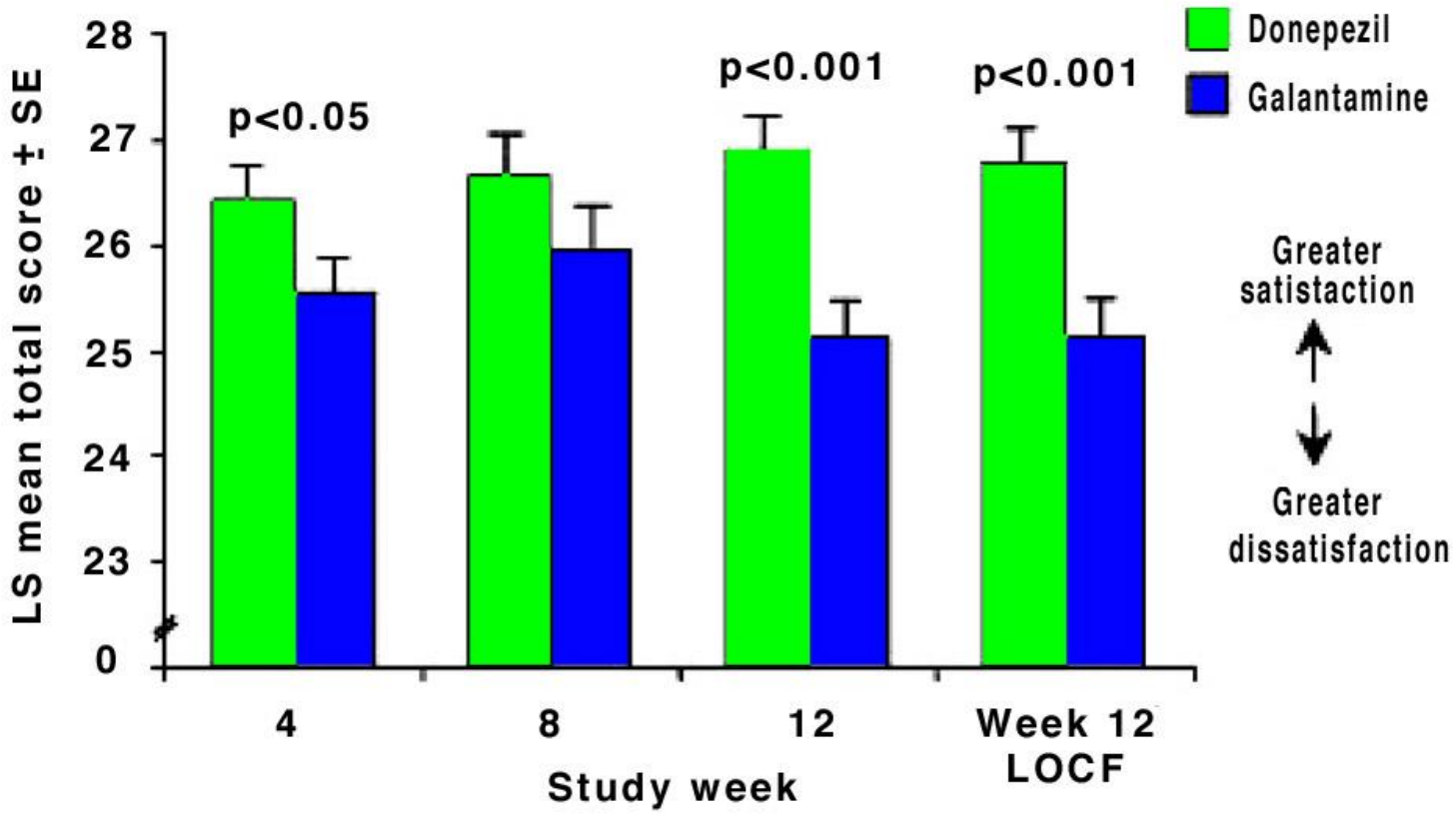
Roy W. Jones[1]*, Hilkka Soininen[2], Klaus Hager[3], Dag Aarsland[4], Peter Passmore[5], The DONGAL Study Group, Anita Murthy[6], Richard [illegible]ng[7] and Ranbir Bahra[7]

[1]*Research Institute for the Care of the Elderly, St M[illegible] Hospital, Bath, UK*
[2]*Department of Neurology, Kuopio University Hospital[illegible]d*
[3]*Department of Medical Rehabilitation and Geriatrics He[illegible]tiftung, Hannover, Germany*
[4]*Rogaland Psykiatriske Sykehus, Stavanger, Norway*
[5]*Department of Geriatric Medicine, Queen's University, Belfast*
[6]*Eisai Inc., Teaneck, New Jersey, USA*
[7]*Pfizer Inc., New York, USA*

Study funded by
Donepezil manufacturer

Jones RW et al. Int J Geriatr Psychiatry 2004;19:58-67

Physician's Satisfaction/Ease of Use Questionnaire Total Score (ITT population)



Donepezil n=60	60	60	(64)
Galantamine n=54	53	52	(56)

Score renges from a minimum of 6 to a maximum of 30

Jones RW et al. Int J Geriatr Psychiatry 2004;19:58-67

SPECIAL ARTICLE

NEJM 12 November 2009

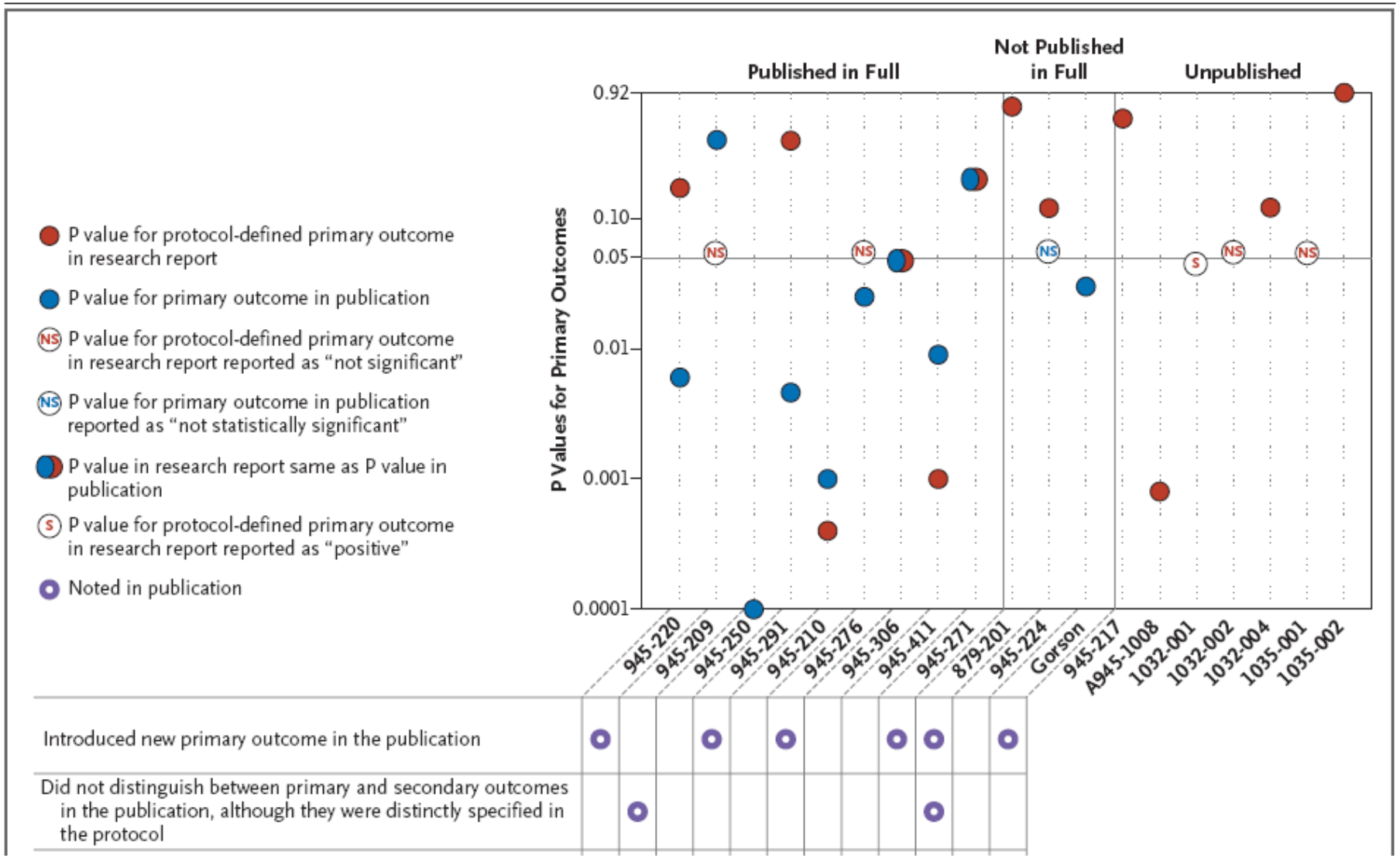
Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

RESULTS

We identified 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis; of these trials, 12 were reported in publications. For 8 of the 12 reported trials, the primary outcome defined in the published report differed from that described in the protocol. Sources of disagreement included the introduction of a new primary outcome (in the case of 6 trials), failure to distinguish between primary and secondary outcomes (2 trials), relegation of primary outcomes to secondary outcomes (2 trials), and failure to report one or more protocol-defined primary outcomes (5 trials). Trials that presented findings that were not significant ($P \geq 0.05$) for the protocol-defined primary outcome in the internal documents either were not reported in full or were reported with a changed primary outcome. The primary outcome was changed in the case of 5 of 8 published trials for which statistically significant differences favoring gabapentin were reported. Of the 21 primary outcomes described in the protocols of the published trials, 6 were not reported at all and 4 were reported as secondary outcomes. Of 28 primary outcomes described in the published reports, 12 were newly introduced.

Changing outcomes …



Today three main topics only:

- Role of systematic reviews (or the risks of publications bias)
- Patients involvement (or information vs persuasion)
- Communicating risks and benefits

Other topics for another meeting:

- EBM, RCTs, independent research, guidelines, research ethics, …

2. Role of reliable evidence

Communicating risks and benefits (and uncertainties)

Quality of published studies/papers

Drummond Rennie,

deputy editor (west), JAMA

Guarding the guardians:

JAMA 1986;256:2391-2

There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print.

ESTABLISHED IN 1812 DECEMBER 12, 2019 VOL. 381 NO. 24

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

Sabue Mulangu, M.D., Lori E. Dodd, Ph.D., Richard T. Davey, Jr., M.D., Olivier Tshiani Mbaya, M.D., Michael Proschan, Ph.D., Daniel Mukadi, M.D., Mariano Lusakibanza Manzo, Ph.D., Didier Nzolo, M.D., Antoine Tshomba Oloma, M.D., Augustin Ibanda, B.S., Rosine Ali, M.S., Sinaré Coulibaly, M.D., Adam C. Levine, M.D., Rebecca Grais, Ph.D., Janet Diaz, M.D., H. Clifford Lane, M.D., Jean-Jacques Muyembe-Tamfum, M.D., and the PALM Writing Group, for the PALM Consortium Study Team*

ABSTRACT

BACKGROUND

Although several experimental therapeutics for Ebola virus disease (EVD) have been developed, the safety and efficacy of the most promising therapies need to be assessed in the context of a randomized, controlled trial.

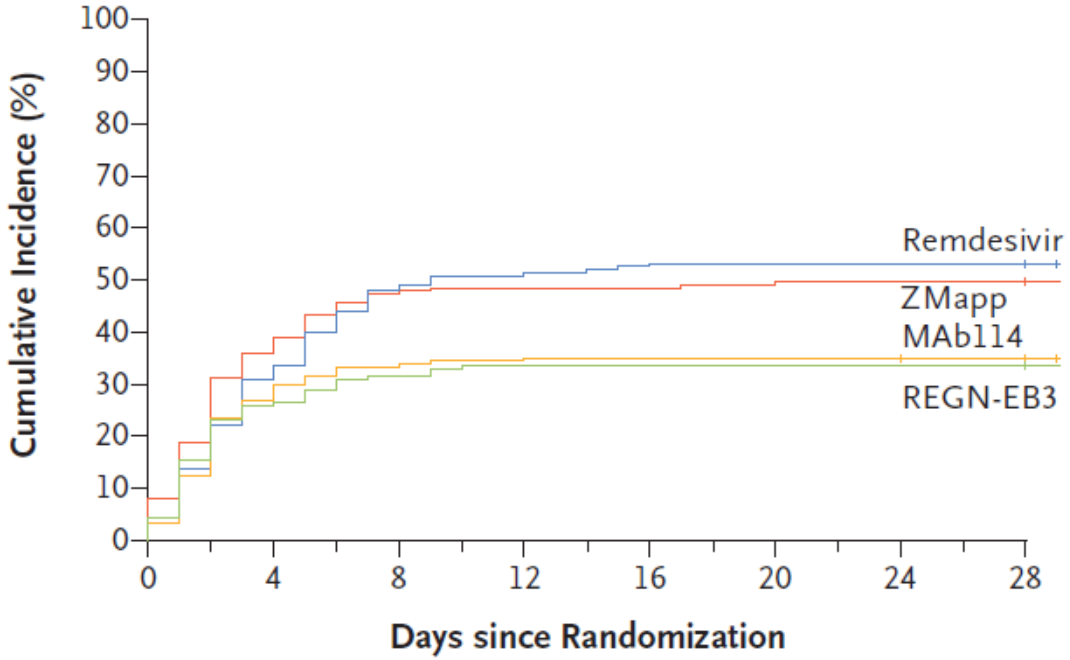
METHODS

We conducted a trial of four investigational therapies for EVD in the Democratic Republic of Congo, where an outbreak began in August 2018. Patients of any age who had a positive result for Ebola virus RNA on reverse-transcriptase–polymerase-chain-reaction assay were enrolled. All patients received standard care and were randomly assigned in a 1:1:1:1 ratio to intravenous administration of the triple monoclonal antibody ZMapp (the control group), the antiviral agent remdesivir, the single monoclonal antibody MAb114, or the triple monoclonal antibody REGN-EB3. The REGN-EB3 group was added in a later version of the protocol, so data from these patients were compared with those of patients in the ZMapp group who were enrolled at or after the time the REGN-EB3 group was added (the ZMapp subgroup). The primary end point was death at 28 days.

RESULTS

From Institut National de Recherche Biomédicale, Democratic Republic of Congo (S.M., O.T.M., D.M., M.L.M., D.N., A.T.O., A.I., R.A., J.-J.M.-T.); the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD (L.E.D., R.T.D., M.P., H.C.L.); the Alliance for International Medical Action, Dakar, Senegal (S.C.); International Medical Corps, Los Angeles (A.C.L.); Epicentre, Médecins sans Frontières, Paris (R.G.); and the World Health Organization, Geneva (J.D.). The full names, academic degrees, and affiliations of the members of the PALM Writing Group are listed in the Appendix. Address reprint requests to Dr. Lane at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Dr., Rm. 4-1479, MSC 1460, Bethesda, MD 20892-1504, or at

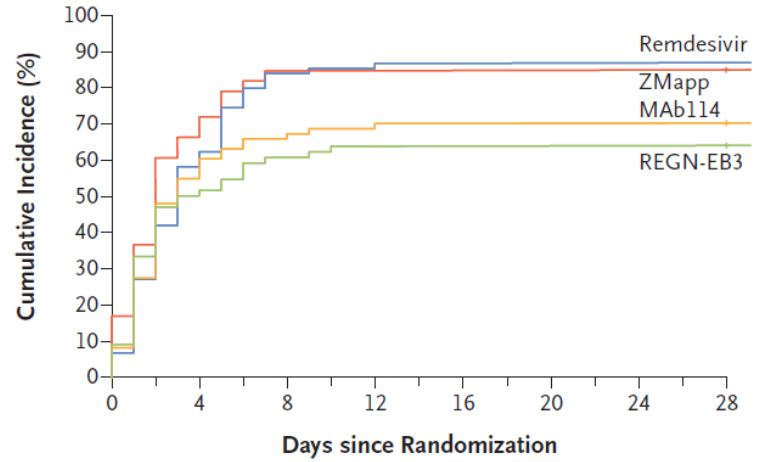
A Incidence of Death, Overall



No. at Risk

ZMapp	169	137	108	96	89	87	87	87	87	86	86	85	85	85	85
Remdesivir	175	151	121	105	91	86	86	85	83	82	82	82	82	82	82
MAb114	174	152	127	119	116	114	114	113	113	113	113	113	113	112	112
REGN-EB3	155	131	115	110	106	104	103	103	103	103	103	103	103	103	103

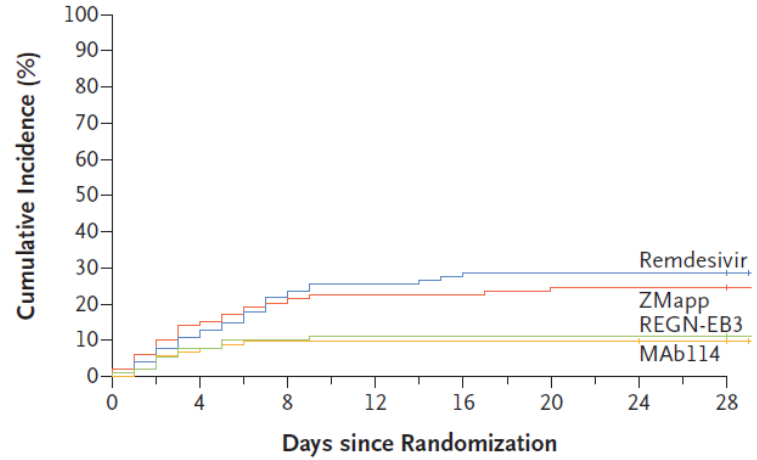
B Incidence of Death, Patients with a High Viral Load



No. at Risk

ZMapp	71	45	24	15	11	11	11	11	11	11	11	11	11	11	11
Remdesivir	75	55	32	20	13	12	12	11	11	11	11	11	11	11	11
MAb114	73	53	33	27	25	23	23	22	22	22	22	22	22	22	22
REGN-EB3	66	44	33	30	26	25	24	24	24	24	24	24	24	24	24

C Incidence of Death, Patients with a Low Viral Load



No. at Risk

ZMapp	98	92	84	81	78	76	76	76	76	75	75	74	74	74	74
Remdesivir	100	96	89	85	78	74	74	74	72	71	71	71	71	71	71
MAb114	101	99	94	92	91	91	91	91	91	91	91	91	91	90	90
REGN-EB3	89	87	82	80	80	79	79	79	79	79	79	79	79	79	79

We encountered numerous challenges in the performance of this trial. It was conducted in a region of the DRC in which there is regional violence, mistrust of government, mistrust of the Ebola response, an unstable electrical power grid, transportation difficulties, and a history of high morbidity from other infectious diseases. Missing results from laboratory tests make the logistic-regression analyses difficult to interpret. … The trial was interrupted temporarily in two participating centers that had to be evacuated because of violence directed against those units by local community or paramilitary groups who were reportedly suspicious of the activities under way in those facilities.

Reaching a successful conclusion to this challenging trial required careful planning as well as the cooperation, support, and coordination of national and international health agencies, government leaders, pharmaceutical companies, dedicated oversight boards, scientists, and nongovernmental organizations. This trial showed that it is possible to conduct scientifically rigorous and ethically sound research during an outbreak, even in a conflict zone.


unicef

3. What's next?

Communicating risks and benefits (and uncertainties)

Communicating risk and benefits … and CoIs

PERSPECTIVE

TRANSPARENCY AND THE DOCTOR–PATIENT RELATIONSHIP

Transparency and the Doctor–Patient Relationship — Rethinking Conflict-of-Interest Disclosures

Eli Y. Adashi, M.D., I. Glenn Cohen, J.D., and Jacob T. Elberg, J.D.

In March 2020, the U.S. Department of Justice (DOJ) brought a lawsuit under the False Claims Act against a major manufacturer of spinal-surgery devices and related entities, accusing the company of paying nearly three dozen spine surgeons a total of more than $8 million in sham consulting payments. The compensation analysis by Kaiser Health News, the same surgeons made up 25% of all U.S. doctors who accepted at least $100,000 from medical device and drug manufacturers in 2020 — and two thirds of those who accepted at least $1 million.[2] Not all such payments are improper or unlawful. But the sheer volume of payments, combined with the fact that many have failed to report relevant payments,[3] These developments substantially enhance the program's potential benefits.

Open Payments places the burden of disclosure on manufacturers, however — not on practitioners. Similarly, when it comes to enforcement of antibribery laws in health care, the DOJ has been

know it exists. We therefore believe it's time to consider whether practitioners should be required to disclose financial relationships directly to patients.

NEJM 27 Jan 2022

Thoughts for new medical students at a new medical school

Richard Smith

Giving advice to medical students makes doctors think about what is important in what they do

BMJ, London WC1H 9JR
Richard Smith
editor

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BMJ 2003;327:1430–3

Earlier this year I had the privilege of speaking to new medical students at a new medical school—the Hull York Medical School. What should I say? I felt almost overawed. It seemed a major responsibility, although I knew that most of what I said would—thankfully—be forgotten or ignored as the ramblings of yet another "old fart." Needing help and a method, I started by asking members of our editorial board, doctors from all over the world, what I should say. They responded with enthusiasm, giving me the thought that it might be a good idea to broaden the debate. That's the main reason for this article: it's a preliminary statement in what I hope might be a rich debate. In thinking what we want to say to new entrants to the profession we have to think of what is important about what we do.

What follows is a mixture of my own ideas and those I selected from the responses of the members of the edi-

I asked the students when I spoke to them, "What was the greatest invention of the 20th century?" Was it quantum mechanics, aircraft, penicillin, the atomic bomb, the double helix, the randomised controlled trial? I suggested (slightly tongue in cheek) that it was D W Winnicott's "the good enough mother." (Actually, it was jazz.) The attempt to be the best mother in the world, the best neurosurgeon, or the best medical editor will end in tears. Being a good enough mother is to be a good mother, whereas the attempt to be the best will guarantee that you won't be (indeed, you may be a highly damaging mother). Similarly, you should aim to be a good enough medical student and doctor.

One of the curses of doctors is that they have such strong stereotypes. Doctors are upstanding, trustworthy, clever, straitlaced, conservative, authoritarian,