PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-Term Efficacy and Safety of IncobotulinumtoxinA and Conventional Treatment of Poststroke Arm Spasticity – a Prospective, Non-Interventional, Open-Label, Parallel-Group Study
AUTHORS	Dressler, Dirk; Rychlik, Reinhard; Kreimendahl, Fabian; Schnur, Nicole; Lambert-Baumann, Judith

VERSION 1 - REVIEW

REVIEWER	Alessandro Picelli Neuromotor and Cognitive Rehabilitation Research Center Department of Neurological, Biomedical and Movement Sciences University of Verona, Italy
REVIEW RETURNED	06-Aug-2015

GENERAL COMMENTS	This open-label study compares the efficacy and safety of BoNT-A (Xeomin) to conventional therapy for upper limb spasticity in 218 patients with stroke. It deals with an argument of potential interest for the readers of BMJ Open. MAJOR ISSUES 1) Botulinum toxin type A is a first-line treatment for post-stroke spasticity in adult patients. This is supported by some international and national guidelines as well consensus conferences and review articles. The Authors clearly stated this concept in the Introduction section (page 4, 19-24). Furthermore, they report that botulinum toxin therapy would not be so routinely used in daily clinical practice. This sounds quite strange to me because, to the best of my knowledge, in Germany botulinum toxin is widely used to treat spasticity in adults as well as in children. So, in my opinion, BoNT-A can be considered as a conventional pharmacological approach for treating spasticity. I recommend to better explain the rationale of this study, because it is quite unclear. OTHER ISSUES 1) OVERALL. As to the level of linguistic quality, minor revisions are needed. 2) OVERALL. Please, do not use commercial names of BoNT-A brands through the whole body of the text. 3) TITLE. In my opinion it would be useful to add some information about the study design. 4) TITLE. Please, do not include the name of commercial brands.

	5) ABSTRACT. Please, remove all abbreviations. 6) ABSTRACT. Please, correct it according to the main changes of the text. 7) KEYWORDS. Please, use only the MeSH terms. 8) KEYWORDS. Please, do not use words included in the title. 9) INTRODUCTION. See the main issues raised above. 10) INTRODUCTION. Page 4, lines 28-32: please, specify your main and secondary outcomes. 11) METHODS. Page 5, PATIENTS: Who decided to treat patients with BoNT-A or not? Patients were included in the INCO or CON group on the base of what? 12) METHODS. Page 5, PATIENTS: no measure of spasticity severity as inclusion criterion (i.e. AS >1)? 13) METHODS. Page 5, PATIENTS: Adult age is not the same in all Countries. Do you mean >18 years? 14) METHODS. Page 5, PATIENTS: What about fixed contractures or previous neurolytic, orthopedic/neurosurgery antispastic procedures as exclusion criteria? 15) METHODS. What about treatment procedures? What about the intensity of rehabilitation procedures? What about casting or splinting? What about the administration of BoNT-A (injection technique, etc). 16) RESULTS. What about homogeneity of the two groups for all the outcomes and rehabilitation procedures? It is not only a matter of treatment, but also of intensity. Please, provide this information 17) DISCUSSION. Please, improve the critical discussion of your results also significantly reducing their repetition. 18) DISCUSSION. Limitations of the study? 19) DISCUSSION. Future perspectives? 20) TABLES. No remarks. 21) FIGURES. No remarks.

REVIEWER	Francesco Panza, MD, PhD Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy
REVIEW RETURNED	19-Sep-2015

GENERAL COMMENTS	Dressler and colleagues, in this prospective, non-interventional, open-label, parallel-group analysis, presented the data of a long-term, multicentre study on the efficacy and safety of incobotulinumtoxinA versus conventional antispastic treatment alone in patients with post-stroke arm spasticity. The Authors found that incobotulinumtoxinA combined with rehabilitation and oral medication produced a much more robust improvement in all aspects of arm spasticity than conventional antispastic treatment, with effects stable over a period of 1 year, and negligible adverse effects. Strenghts of the present real-world study included the large sample coming from a multicentre his is the largest study of its kind. This is a well-written and well-conducted study dealing with an argument of interest for the BMJ Open readers. I suggest some minor changes to clarify some methodological issues: 1. Methods: Did you include first-ever stroke patients? Unilateral or bilateral stroke? 2. Methods: The Authors should clarify the lower age limit among the inclusion criteria.

	3. Methods: The Authors should clarify the injection techniques (ultrasound-guided, manual needle placement, EMG-guided, etc) used in the post-stroke patients for the treatment with incobotulinumtoxinA in the different study sites or within each centre. 4. Discussion: The Authors should include a paragraph devoted to the description of the principal limitations of the study, including the percentage of specialist physicians in the incobotulinumtoxinA arm compared to the percentage in the conventional therapy arm, discussion of the non-interventional design of the study and its possible influence on the suggested findings, differences in the injection techniques used in the post-stroke patients in different study sites (J Neurol Sci. 2014;347:39-43), and other possible methodological differences among different study sites possibly influencing study findings. The Authors should also discuss the impact of these and other limitations on the generalizability of the findings given also the non-interventional design of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
MAJOR ISSUES
An analysis of claims data from a large statutory German health insurance fund surprisingly found that none in the cohort received BT treatment for poststroke spasticity (reference 7) and thus BT cannot as yet be considered a conventional treatment for poststroke spasticity. We amended the corresponding paragraph accordingly.

OTHER ISSUES
1. The text was amended.
2. The commercial name of incobotulinumtoxinA was used once on page 4 under Methods as an explanation for readers unsure about brand and generic names of different botulinum toxin type A preparations. If possible, we would prefer to keep this. The brand name was, however, deleted in the title of the manuscript.
3. The study design was added to the title.
4. The brand name was deleted from the title.
5. Abbreviations were removed and the text amended.
6. We amended the section ‘main outcome measures’ but retained the additional assessment parameter as word limit permitted this.
7. The list of keywords was amended.
8. Title words were removed.
9. Text was changed; please see our response under major issues.
10. We were uncertain, if the reviewer wanted us to specify the outcome parameters or the results. We added the former to the introduction.
11. General practitioners and specialists were asked if they wanted to participate in this study. Before start of study they had to indicate how they wanted to treat their patients for spasticity and were thus included in the INCO or the CON study arm. For non-interventional studies, the decision how to treat a patient has to be made before the patient is included in the study. Treatment decisions are solely at the discretion of the treating physicians. The paragraph was amended for clarification.
12. Patients could be included if they had a diagnosis of poststroke arm spasticity and a need for antispastic treatment. The degree of severity for inclusion was not specifically predefined, since an indication for antispastic treatment was mandatory.
13. Yes; this was amended in the text.
14. Due to the non-interventional design these patients were not excluded.

15. Any antispastic treatment was documented, but data regarding intensity of procedures, casting or splinting and different administration techniques of BoNT/A (ultra-sound or EMG-guided etc.) were not obtained.
16. Due to the different kinds of procedures, we did not obtain the intensity of methods applied. This was amended in the text.
17. Parts of the discussion were rewritten.
18. A paragraph was added.
19. Text was added at the end of the discussion.

Reviewer: 2
1. The inclusion criteria in this non-interventional trial were not chosen to discriminate between first-ever or secondary stroke. Also the inclusion of patients was not limited to unilateral or bilateral stroke, since our intention was to catch real-world treatment of poststroke arm spasticity.
2. Lower age limit was included under the section 'Patients'.
3. As this was a comparison between BT treatment and conventional therapies, physicians were not asked about their BT injection techniques.
4. A new paragraph was added. The BT injection technique used is in our opinion not relevant to the study question, as we compared BT treatment to conventional therapy.

VERSION 2 – REVIEW

REVIEWER	Alessandro Picelli Neuromotor and Cognitive Rehabilitation Research Center Department of Neurological, Biomedical and Movement Sciences University of Verona, Italy
REVIEW RETURNED	27-Oct-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.