Equivalence and non-inferiority testing in psychotherapy research

Falk Leichsenring¹, Allan Abbass², Ellen Driessen³, Mark Hilsenroth⁴,
Patrick Luyten⁵,⁶, Sven Rabung⁷ and Christiane Steinert¹,⁸

¹Department of Psychosomatics and Psychotherapy, Justus-Liebig-University Giessen, Ludwigstr 76, D-35392 Giessen, Germany; ²Department of Psychiatry, Dalhousie University, Centre for Emotions and Health, Halifax 8203-5009 Veterans Memorial Lane, Halifax, NS B3H 2E2, Canada; ³Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands; ⁴Dermer School of Psychology, Adelphi University, Hy Weinberg Center, 1 South Avenue, Garden City, NY 11530-0701, USA; ⁵Faculty of Psychology and Educational Sciences, University of Leuven, Klinische Psychologie (OE), Tiensestraat 102 – bus 3722, 3000 Leuven, Belgium; ⁶Research Department of Clinical, Educational and Health Psychology, University College London, Gower Street, London WC1E 6BT, UK; ⁷Department of Psychology, Alpen-Adria-Universität Klagenfurt, Universitätsstr, 65-67, A-9020 Klagenfurt, Austria and ⁸Department of Psychology, MSB Medical School Berlin, Calandrellistr. 1-9, 12247 Berlin, Germany

With more than 100 non-inferiority or equivalence trials published per year in many areas of research (Piaggio et al., 2012), statistical and methodological issues involved in these trials become increasingly important. A recent article by Rief and Hofmann (2018) suggests, however, that some of these issues are not sufficiently clear. For this reason, central issues will be discussed here and some misunderstandings will be addressed.

Equivalence and non-inferiority margins

For defining a non-inferiority or equivalence margin (i.e. the minimum difference important enough to make treatments non-equivalent), no generally accepted standards exist. In 332 equivalence or non-inferiority medical trials, a median margin of 0.50 standard deviations was found (Lange and Freitag, 2005), corresponding quite well to the value of 0.42 reported by Gladstone and Vach (2014). Only five studies used margins < 0.25 (Gladstone and Vach, 2014) and only 12% of studies margins ≤0.25 (Lange and Freitag, 2005).

In psychotherapy research, margins ranging from 0.24 to 0.60 have been proposed (e.g. Steinert et al., 2017, p. 944). In a meta-analysis of psychodynamic therapy (PDT) including different mental disorders, Steinert et al. (2017) chose a margin of $g = 0.25$, which is among the smallest margins ever used in psychotherapy and medical research (Gladstone and Vach, 2014, Figure 2, Steinert et al., 2017, p. 944). This margin is very close to both (a) the threshold for a minimally important difference specifically suggested for depression (0.24, Cuijpers et al., 2014), and (b) the margin recommended by Gladstone and Vach (2014) to protect against degradation of treatment effects in non-inferiority trials ($d = 0.23$).

In their recent correspondence article, Rief and Hofmann (2018) make a quite different proposal, recommending margins not to fall below 90% of the uncontrolled effect size of the established treatment. This proposal, however, is associated with several problems described in more detail in Table 1, particularly regarding the clinical significance of the suggested margin and its implications for sample size determination, rendering non-inferiority trials in psychotherapy research virtually impossible (Table 1).

Statistical hypotheses in equivalence and non-inferiority testing

In equivalence testing, the null and alternative hypotheses of superiority testing are reversed and the statistical alternative hypothesis is consistent with the assumption of equivalence (Lesaffre, 2008; Walker and Nowacki, 2011). To test for equivalence, two one-sided tests are performed determining whether the upper and the lower boundary of the CI are included in the margin, whereas, for testing non-inferiority, one one-sided test inspecting the lower boundary is used (Lesaffre, 2008; Walker and Nowacki, 2011). A statistically significant result implies here that the effect size and its CI are within the margin, demonstrating equivalence or non-inferiority (Walker and Nowacki, 2011). A recent meta-analysis testing equivalence of PDT to other approaches established in efficacy reported a significant result indicating that the effect sizes and their CIs were completely included in the margin (Steinert et al., 2017). Thus, the recently given interpretation by Rief and Hofmann (2018, p. 2) that Steinert et al. (2017) ‘… found a significant disadvantage of PDT [psychodynamic therapy] compared with other treatments (including CBT)’ is simply wrong (Lesaffre, 2008; Walker and Nowacki, 2011).
**Table 1.** Further methodological issues of equivalence and non-inferiority testing

| (a) Minimal important difference | A margin needs to reflect a minimal important difference and some small difference may not be clinically meaningful (McGlothlin and Lewis, 2014). Rief and Hofmann (2018) recommended margins not to fall below 90% of the uncontrolled effect size of the established treatment. For an uncontrolled effect size of \( d = 0.5 \), for example, Rief and Hofmann’s proposal implies a very small margin of 0.05. This margin corresponds to differences, for example, in the Hamilton Rating Scale for Depression and the Hamilton Anxiety Rating Scale of 0.28 and 0.35 scale points which can hardly be considered clinically relevant. As shown above, most researchers agree on larger margins (Lange and Freitag, 2005; Gladstone and Vach, 2014; Steinitz et al., 2017). |
| (b) Sample size | Furthermore, Rief and Hofmann’s proposal for demonstrating non-inferiority with a power of 0.80 using a margin of \( d = 0.05 \) and applying one-sided test at \( \alpha = 0.025 \) (Lesaffre, 2008), would require \( 2 \times 681 \) subjects. In psychotherapy research, sample sizes like this can hardly be realized, rendering non-inferiority trials in this field virtually impossible. |
| (c) Intent-to-treat analyses | Whether intent-to-treat analyses compensating for missing data carry the risk of diluting treatment differences in non-inferiority trials (Rief and Hofmann, 2018, p. 2) is also open to further research (Lesaffre, 2008; Walker and Nowacki, 2011). |
| (d) Efficacy of the comparator (assay sensitivity) | From the relatively low response rates reported by two studies (Driessen et al., 2013; Connolly Gibbons et al., 2016), Rief and Hofmann concluded that the comparator (CBT) may not have been adequately implemented to reach its typical therapeutic effects. However, this claim is not supported by evidence for several reasons: |
| | • Concluding from the results of a study which do not meet the researcher’s expectation that its quality was low is scientifically questionable. Results contradicting the researcher’s hypothesis may provide important information. Poor study quality needs to be demonstrated independently of study results. |
| | • In fact, the studies by Connolly Gibbons et al. (2016) and Driessen et al. (2013) included CBT supervisors to ensure adequate implementation of CBT. The adequate treatment fidelity ratings of both studies support the notion that the comparator was adequately implemented. |
| | • The study by Connolly Gibbons et al. (2016) was a community study for which lower response rates are common. For instance, Persons et al. (1999) found that only 17% of patients receiving CBT in primary care showed both reliable change and clinically significant change. In the Connolly Gibbons trial, 28% of CBT patients met criteria for both, indicating that CBT delivered in this study was effective. |
| | • Thus, there is no evidence that in these studies low-effective versions of CBT were implemented favouring non-inferiority. |
| (e) Researcher allegiance | Researcher allegiance has a major impact on comparative psychotherapy outcome research (Munder et al., 2013). It is highly relevant for both superiority and equivalence testing. For this reason, Steinitz et al. (2017, p. 945, 947), for example, controlled for researcher allegiance both at a statistical and an experimental level by including representatives of both PDT and CBT (adversarial collaboration). In spite of these careful procedures, Rief and Hofmann (2018, p. 2) suggest that the interpretation of study results was influenced by the financial sponsor of the study. Steinitz et al. (2017, p. 951), however, clearly stated that the sponsor did not have any influence on the design, the evaluation, and the interpretation of this meta-analysis. Furthermore, an adversarial collaboration was established precisely to prevent allegiance effects. This is true for the included studies by Driessen et al. (2013) and Connolly Gibbons et al. (2016) too. |
| (f) Equivalence testing v. number of studies | Rief and Hofmann (2018, p. 2), state that due to the larger number of studies available for a specific therapeutic approach (CBT) the CIs of the effect sizes for this approach are smaller than those for other approaches. They use this point to argue that success would be more reliably achieved with CBT, even if equivalence had been demonstrated. This argument is questionable for several reasons: |
| | • Equivalence testing is confused here with issues of reliability. |
| | • Only the CIs of randomized head-to-head comparisons may be directly compared, otherwise study conditions may differ. |
| | Taking risk of bias into account, the large number of CBT studies shrinks to 11 low-bias studies for depression and 21 studies for anxiety disorders (Cuipers et al., 2016). For this reason, Cuipers et al. (2016, p. 245) concluded that the effects of CBT are ‘uncertain and should be considered with caution’, implying less confidence in the effects of CBT than suggested by Rief and Hofmann (2018). |
| (g) (Deductive) hypothesis testing v. inductive conclusions | Steinitz et al. (2017) tested the hypothesis that psychodynamic therapy is as efficacious as treatments with established efficacy. This hypothesis was corroborated in a strict test that included a small margin, a control of researcher allegiance, and adequately implemented comparators established in efficacy (Steinitz et al., 2017). Steinitz et al. (2017) have never claimed that their results may be inductively generalized to conditions for which no studies of PDT exist such as insomnia as suggested by Rief and Hofmann (2018). |

---

*Paul Crits-Christoph, personal communication, 16 February 2018.
Paul Crits-Christoph, personal communication, 26 February 2018.
Equivalence v. non-inferiority testing

Equivalence and non-inferiority testing need to be differentiated (Treadwell et al., 2012). In non-inferiority testing, for example, the test treatment is expected to be superior to the standard treatment in measures not related to efficacy such as side effects or costs (Treadwell et al., 2012). Rief and Hofmann did not make this differentiation. In fact, the meta-analysis by Steinert et al. (2017), for example, was a test of equivalence, not of non-inferiority as suggested by Rief and Hofmann (2018).

Assay sensitivity and constancy of study conditions

Equivalence and non-inferiority testing require that the efficacy of the comparator is ensured and that the study conditions are comparable with in which the efficacy of the comparator was established (Treadwell et al., 2012). In those context, Rief and Hofmann (2018) claim that specific issues of (low) study quality favour non-inferiority results, e.g. low response rates found in specific studies or low treatment integrity. Again, however, these claims are not supported by evidence (Table 1). This applies to several further issues put forward by Rief and Hofmann (2018) which are briefly discussed in Table 1, for example to the relationship between equivalence testing and the number of studies available for a specific treatment (Table 1).

Conclusions

Equivalence and non-inferiority testing pose specific methodological problems (Piaggio et al., 2012; Treadwell et al., 2012), for example, in defining a margin, statistical testing, and ensuring the efficacy of the comparator or comparability of study conditions (Table 1). Conclusions about equivalence and non-inferiority testing differing from Rief and Hofmann’s (2018) are presented which are more consistent with the available evidence and usual standards across a range of scientific disciplines.

References

Connolly Gibbons MB et al. (2016) Comparative effectiveness of cognitive therapy and dynamic psychotherapy for major depressive disorder in a community mental health setting: a randomized clinical noninferiority trial. JAMA Psychiatry 9, 904–911.


