

1 **Title**

2

3 How the EMERGE guideline on medication adherence can improve the quality of clinical trials

4

5 **Short title**

6 Using EMERGE to inform drug trial protocols

7

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32

33 **Abstract**

34 Medication adherence in drug trials is suboptimal, affecting the quality of these studies and  
35 adding significant costs. Non-adherence in this setting can lead to null findings, unduly large  
36 sample sizes, and the need for dose modification after a drug has been approved. Despite  
37 these drawbacks, adherence behaviours are not consistently measured, analysed or reported  
38 appropriately in trial settings. The ESPACOMP Medication Adherence Reporting Guideline  
39 (EMERGE) offers a solution, by facilitating a sound protocol design that takes this crucial factor  
40 into account. This article summarises key evidence on traditional and newer measurements  
41 of adherence, discusses implementation in clinical trial settings, and makes recommendations  
42 about the analysis and interpretation of adherence data. Given the potential benefits of this  
43 approach, the authors call on regulators and the pharmaceutical industry to endorse the  
44 EMERGE guideline.

45

46 **Key words**

47 Adherence; Clinical trials, Pharmacokinetic-Pharmacodynamic

48 **[Heading 1] Introduction**

49 Adherence to treatment should be reported in all clinical trials. This call has been repeated  
50 for more than 20 years [1-4] but unfortunately, proper consideration of adherence remains  
51 the exception rather than the rule. Too often, adherence is neglected at every stage of the  
52 research process, from trial design and conduct through to data analysis and reporting in the  
53 literature. The consequences are concerning. If adherence is prevalent and unrecognised in a  
54 trial, it can potentially confound safety and efficacy signals, and obscure exposure-response  
55 estimations [1-4]. If we do not know whether patients followed their treatment accurately  
56 during a trial – and why they did so, or why they did not – our understanding of how the drug  
57 will work in clinical practice may be dangerously flawed.

58

59 Until recently, the lack of concise guidance on how adherence should be measured, analysed  
60 and reported in clinical trials has been a barrier. Now, the International Society for Medication  
61 Adherence (ESPACOMP) Medication Adherence Reporting Guideline (EMERGE) offers a  
62 solution [5].

63 This is a tool that can readily be applied alongside recommendations from the US Food and  
64 Drug Administration (FDA) [6] and the European Medicines Agency (EMA) [7]. EMERGE has  
65 also been designed to complement the Consolidated Standards of Reporting Trials (CONSORT,  
66 for randomised controlled trials) [8] and the Strengthening the Reporting of Observational  
67 Studies in Epidemiology (STROBE) standards [9].

68

69 In addition to complementing existing clinical trial guidelines, EMERGE aims to increase  
70 transparency and consistent reporting on adherence by offering a list of 21 items that include  
71 minimum reporting criteria, and more detailed recommendations for each element of a  
72 research report (the abstract; introduction; methods including study design and participants,  
73 measurement, intervention and statistical analysis; results; and discussion) [5].

74

75 The EMERGE development methodology has been previously reported [5]. In brief, the  
76 guideline was developed through a Delphi process involving an international panel of experts.  
77 The group followed the recommended procedure outlined by the Enhancing the QUALity and  
78 Transparency Of health Research (EQUATOR) group [10]. Like other reporting guidelines,  
79 while EMERGE offers a list of essential criteria, it does not extend to providing methodological  
80 recommendations.

81

82 This paper thus has a dual aim. It provides a comprehensive summary of recommendations  
83 for measurement, analysis and interventions related to treatment adherence in drug trial  
84 settings. When used in combination with EMERGE, this paper can guide trial sponsors and  
85 researchers as they develop drug trial protocols aligned with other key guidelines, which  
86 specify that participants' adherence to investigational products and trial protocols should be  
87 adequately reported [8,11]. It is also a call to pharmaceutical regulators to take decisive action  
88 to officially endorse EMERGE and to give appropriate consideration of adherence and its  
89 impact on drug development [5]. Clear guidance from regulatory approval organisations is  
90 key to driving change in the pharmaceutical industry.

91

92 **[Heading 1] Background**

93

94 Non-adherence to appropriately prescribed treatments is a substantial and costly problem  
95 that can severely impact both trials and practice, through reduced clinical benefit and  
96 increased risk of morbidity and mortality [12, 13]. In clinical practice, up to 50% of patients  
97 do not take their medications as prescribed [14] and estimates point to non-adherence  
98 accounting for up to 48% of asthma deaths, an 80% increased risk of death in diabetes and a  
99 3.8-fold increased risk of death in the year following a heart attack [15]. The related cost to  
100 health care systems across the world is substantial: the cost of unused medicines has been  
101 estimated to reach £300 million per year in the United Kingdom [16].

102 Adherence in clinical trial settings is also suboptimal. Blaschke et al. (2012) compiled  
103 adherence data captured by electronic measurements from 16,907 participants across 95  
104 clinical trials. They found an initial drop of 4% due to non-initiation. By day 100, 20% of  
105 participants were non-persistent (i.e. had stopped taking treatment against protocol  
106 specifications) and, among persistent patients, daily, a further 15% displayed sub-optimal  
107 implementation [17].

108 However, assessment and reporting of adherence and drug discontinuation in clinical trials is  
109 lacking. One recent systematic review of medication adherence in RCTs evaluating  
110 cardiovascular or mortality outcomes in dialysis patients found that, of 22 clinical trials that  
111 met the inclusion criteria, only five reported measuring individual-level medication adherence  
112 [18]. All five of these trials also presented results demonstrating negative study outcomes for  
113 the medication under investigation.

114 A striking example of the impact of adherence on efficacy comes from a set of randomised  
115 controlled trials (RCTs) assessing pre-exposure prophylaxis (PrEP) to reduce the risk of  
116 acquiring human immunodeficiency virus (HIV). Corneli et al. (2014) report that, after PrEP  
117 had been found to be effective in three separate RCTs in high-risk populations, two placebo-  
118 controlled RCTs conducted with women at higher risk of acquiring HIV failed to show  
119 effectiveness and were therefore closed early. [19]

120

121 However, when the data were re-analysed using a composite adherence score, based on  
122 plasma and intracellular drug concentrations, it was apparent that only 12% of participants  
123 had achieved good adherence throughout their study participation [19]. This finding raises  
124 the possibility that participants in the trial were not taking enough of the prescribed dose to  
125 see a therapeutic effect.

126

127 The authors used drug concentration as a measure of adherence, instead of pill count or  
128 self-reporting, because they had previously observed that adherence was strongly  
129 overestimated with these measures. Good adherence was defined as plasma and  
130 intracellular concentrations that could be expected if a participant had taken the study drug  
131 four or more times each week over the preceding 28 days.

132

133 Medication non-adherence in clinical trials also results in increased variability and decreased  
134 effect size. The consequences vary, depending on the study design. In placebo-controlled  
135 trials, non-adherence results in decreased power, increasing the risk of type II error (the  
136 failure to show that an effective drug is effective). In positive controlled trials, there is an  
137 increased risk of type I error (erroneously claiming that drugs are equivalent).

138

139 Reduced power is often mitigated by increasing the sample size, which comes at a cost to the  
140 sponsor, or by increasing the dose, which can increase unexpected adverse reactions. Partial  
141 adherence may also cause adverse events due to rebound effects.

142

143 Trials that fail to show effectiveness because of non-adherence may be a widespread issue,  
144 and this suggestion is supported by the published evidence [20-23] However, because  
145 adherence has not been measured and reported appropriately in trial settings, and because  
146 there is a tendency towards under-publication of failed trials, the data are obscured and we  
147 cannot truly know how many compounds have been affected by this problem throughout the  
148 history of drug development.

149

150 Non-adherence may also confound dose-response estimations and skew results towards  
151 overestimation of dosing requirements, which increases the risk of post-approval dose  
152 reductions [3]. Indeed, it has been estimated that 20-33% of all drugs approved since 1980  
153 have been dose-adjusted after market authorisation had been granted, and that 60-80% of  
154 the adjustments were dose reductions [24, 25].

155

156 When a compound fails to reach regulatory approval as a result of non-adherence in clinical  
157 trials, the cost is likely to run into hundreds of millions of dollars annually in the US, and this  
158 cost is primarily carried by the pharmaceutical sponsor. An analysis by the Tufts Center for  
159 the Study of Drug Development suggested that the average cost of getting a drug approved  
160 is \$2.6 billion [26]. Wasted costs are incurred when additional participants are enrolled to  
161 account for non-adherence. There may be opportunity costs, due to missed therapeutic  
162 effect. There will also be a knock-on effect on patients and health care systems, because  
163 otherwise effective treatments are lost. To the best of our knowledge, the downstream  
164 financial impact of post approval dose reductions, and suspended and revoked licences, has  
165 not yet been estimated. However, these costs are likely to add up to substantial losses for the  
166 licence holders [27].

## 167 **[Heading 1] Identifying appropriate adherence measures**

168 As outlined above, comprehensive evidence supports the argument that adherence to  
169 investigational drugs should always be appropriately measured, analysed and reported in all  
170 clinical trials. This section provides guidance to researchers on how to achieve this in  
171 alignment with EMERGE guideline [5]. It will discuss different approaches to measuring  
172 adherence, and explain how EMERGE could be applied in each case.

173 There are advantages and disadvantages with all measures of adherence, and identifying the  
174 measurement most appropriate to any specific trial requires thorough consideration of the  
175 overall objectives, study design and patient population, and the points where adherence may  
176 have an impact on the trial objectives.

177

178 **[Heading 2] The ABC taxonomy**

179 The first step is to identify the specific aspect(s) of adherence that must be captured. The ABC  
180 taxonomy, which is fundamental in EMERGE, defines adherence as a three-phased process by  
181 which patients take their medications as prescribed [5, 28]. Each phase is unique and must be  
182 specifically defined, measured and analysed:

- 183 • A) Initiation is when the patient takes the first dose of a prescribed drug; the process  
184 then continues with
- 185 • B) implementation, which is defined as the extent to which a patient’s actual dosing  
186 corresponds to the prescribed dosing regimen, from initiation until the last dose is  
187 taken; and
- 188 • C) discontinuation marks the end of therapy, with the period between initiation to  
189 discontinuation referred to as persistence.

190 Non-adherence can thus arise in a number of situations, including late- or non-initiation of  
191 prescribed treatment, sub-optimal implementation of the dosing regimen, and non-  
192 persistence/early discontinuation that is not specified by the trial protocol or prescription (see  
193 Figure 1, adapted to clinical trials based on Vrijens et al 2012 [28]).

194

195 The appropriate operational definition(s) of adherence, and how this can be captured, must  
196 be decided. Researchers also need to consider whether it is important to understand any  
197 reasons for non-adherence within their trial populations, which can only be captured by using  
198 patient-reported outcome measures (PROs).

199 **[INSERT FIGURE 1]**

200

201 **[Heading 2] Specific measurements of adherence**

202 The second step is to identify and review potential methods of measurement, taking into  
203 consideration validity, reliability and potential bias of each measure, as well as burden on  
204 participants and investigators. Table 1 presents a summary of each measurement approach  
205 noting key considerations. Further description is provided in the specific sections below.

206

207 **Directly observed therapy (DOT).** This is one of the only real-time measures of adherence  
208 that can guarantee drug ingestion or administration. DOT is resource intensive and primarily  
209 viable where participants are staying in a clinical setting during the trial period. DOT is  
210 therefore often used in Phase I trials with healthy volunteers, but rarely used in Phase II-Phase  
211 IV trials with ambulatory patients. McCann et al. (2015) summarised 'DOT-proxy' methods,  
212 including using camera/video enabled mobile phone technology where participants record  
213 ingestion and transmit the images to investigators for observation [29] (e.g. AiCure  
214 Technologies, Inc.), which may be somewhat burdensome for both parties. DOT methods  
215 could be used to assess all three phases of non-adherence in the clinical trial setting, as  
216 defined by EMERGE. However, the high burden on participants, and the intrusiveness into  
217 their lives, precludes widespread use.

218

219 **Pill count.** Counting returned tablets is the standard practice for drug accountability in clinical  
220 trials: it is also the most commonly used method to measure adherence. However, it is easily  
221 censored by participants and only provides an aggregate summary of adherence between visit  
222 periods. It does not allow precise estimates of initiation, implementation or persistence [30,  
223 31].

224

225 **Patient reported outcome measures.** Self-reported adherence data is also common and is  
226 typically based on a patient-reported outcome (PRO) scale or categorical measure, or as a  
227 patient diary. There are many self-report measures and different methods of administration,  
228 with large variation in validity and reliability, burden to participants and investigators [32,33]  
229 and large variation in licensing fees. PROs are sensitive to recall and social desirability biases



230 and, like pill-count, have often been found to overestimate adherence [17]. Classic  
231 administration traditionally uses pen and paper, which may have increased such biases, but  
232 there has been a move in recent years towards electronic data capture in clinical trials.

233

234 A great advantage of self-report, which is often overlooked in the literature on adherence  
235 measurements, is that it is the only way to explore *why* a participant has acted in a certain  
236 way regarding treatment and/or trial protocol adherence [30,32]. This approach can be  
237 helpful in determining reasons for non-adherence during initiation of therapy,  
238 implementation, and ongoing persistence, providing valuable and timely insight to the drug  
239 development and study design team. Structured or semi-structured PROs can be designed to  
240 capture participants' reasons for non-adherence [32]. However, measures that use double-  
241 barrelled items to capture both the act and cause of non-adherence in one item are not  
242 recommended, as the data would be difficult to interpret.

243

244 Exit interviews are increasingly used to assess adherence, and the reasons for non-adherence,  
245 in a clinical trial setting. A study by Nunn et al. (2016) provides a useful example. In people  
246 diagnosed with HIV, who were stabilised on anti-retroviral treatment, this trial assessed the  
247 risks and benefits of stopping cotrimoxazole (a prophylaxis against opportunistic infections)  
248 [34]. Exit interviews were used to assess participants' adherence to the study procedures. It  
249 emerged that some participants were non-adherent to the trial protocol because they  
250 obtained and used open-label cotrimoxazole, although not to the extent that the trial results  
251 were seriously compromised [34].

252

253 ***Drug or drug metabolite monitoring.*** Monitoring drug or drug metabolites in plasma, urine  
254 or hair can provide a snapshot of adherence. However, such monitoring is sensitive to bias  
255 when participants ingest the investigational drug before a trial visit, even if they may have  
256 been non-adherent in the period running up to the visit (white-coat adherence) [35].  
257 Monitoring the investigational drug in biologic fluids is also restricted to active arms of the

258 trial, unless an ultralow dose of the drug, which is detectable but below the lower end of the  
259 therapeutic range, is used in the control arm [29]. An alternative is to use other  
260 pharmacologically inactive biologic markers that are ingested simultaneously with the  
261 investigational or placebo compounds. The ideal marker should have an appropriate  
262 pharmacokinetic profile in terms of dosing schedule, low variability within and between  
263 participants, few drug-drug or food interactions, and should be excreted in urine or saliva. It  
264 is also essential that the marker is generally considered safe or licensed for use by regulators,  
265 and uncommon in dietary sources, supplements and pharmaceuticals [36]. Another potential  
266 drawback is that the biological marker would need to be added to the formulation of the  
267 investigational drug. [3] This method could be used as a measure of adherence  
268 implementation, given the drawbacks mentioned above are addressed, but it cannot be used  
269 to determine initiation or persistence, unless daily sampling is undertaken.

270

271 ***Electronic detection of package entry.*** Electronic monitoring incorporated in medication  
272 packaging, pioneered by the Medication Event Monitoring System (MEMS®, AARDEX Group,  
273 see [37]), allows for date and time stamped recordings when the participant opens the  
274 pharmaceutical package. MEMS was originally designed as an electronic cap to capture the  
275 opening and closing of a standard pharmaceutical bottle. The principle can easily be extended  
276 to other drug delivery systems, including blister packaging, injections and inhalers. To date,  
277 more than 810 papers in peer-reviewed journals report diverse uses of MEMS in research  
278 settings and a multitude of companies offer smart packaging.

279

280 It is assumed that a correct dose of the investigational drug is ingested each time the  
281 packaging is opened, and that the continuous data captured will clearly display adherence  
282 patterns over time. These recording devices require minimal management from participants  
283 and investigators. Electronic detection of package entry is an indirect measure of dose intake  
284 and there could be instances where the package is activated but a dose is not taken. [31]  
285 Studies comparing MEMS data with drug concentrations show that there is 97% accuracy

286 between opening the pharmaceutical package and time of ingestion of the prescribed dose  
287 [3].

288 In drug trials, this method can be used to precisely identify the time of initiation and the time  
289 of eventual treatment discontinuation. Furthermore, it allows reliable and sound compilation  
290 of each patient's implementation of the dosing regimen.

291

292 ***Ingestible sensors (breath inhaler, smart pill) and electronic detection of ingestion.***

293 Technological approaches to measuring adherence are emerging at a rapid rate. These  
294 include breathalysers (i.e. SMART®; Xhale, Inc.), monitors for inhalers (i.e. the Inhaler  
295 Compliance Assessment; INCA™), and ingestible sensors (i.e. Proteus Digital Health, Inc. and  
296 eTectRx, Inc.). Each can be used to assess adherence across the initiation, implementation  
297 and persistence stages of the clinical trial data collection process that are described in  
298 EMERGE. Many can confirm that the drug has been ingested by the participant, although  
299 some sensors have technical limitations and, alternatively, allow users to record an event by  
300 pressing a button [38]. These measures may also provide insights into patterns of adherence  
301 and non-adherence, although they may not be feasible when investigating specific drugs or  
302 in all contexts of use. For example, ingestible sensors can only be used with solid oral  
303 medication and require drug reformulation. In addition, where a skin patch is required to  
304 detect the signal, the user must maintain the patches over the treatment period: skin  
305 irritation and inflammation are commonly reported [38]. Ingestible sensors may also be  
306 perceived as intrusive by users [39].

307

308 ***Claims and refills.*** Measures such as pharmacy refill and insurance claims data, which are  
309 used in adherence research, are not appropriate in a Phase I-III clinical trial setting where  
310 participants tend to be given the investigational drug during trial visits and the cost of the  
311 treatment is funded by the sponsor. This approach may only be relevant for studies in the  
312 post-approval stage, that is, Phase IV registry studies. In addition, such data do not provide  
313 information on any errors related to dose and timing of administration, which is crucial in  
314 terms of understanding exposure-response [3].

315

316 **Multiple complementary measures.** A trial design that aligns with EMERGE by considering  
317 appropriate definitions of the aspect(s) of adherence to be captured (initiation,  
318 implementation and persistence), may prompt the need for multiple complementary  
319 adherence measures. The use of complementary measures is distinct from measurement  
320 triangulation, in that each measure should measure a distinct element of adherence, and each  
321 should be defined and reported according to EMERGE [5].

322

323 **[INSERT TABLE 1]**

324 **[Heading 1] Adherence interventions in trial settings**

325 Regulators have taken notice of the potential benefit of supporting adherence in trial settings.  
326 The FDA’s guidance for Enrichment Strategies for Clinical Trials to Support Approval of Human  
327 Drugs and Biological Products (2019) acknowledges that good adherence in a trial can  
328 increase the power of a study –its ability to demonstrate a treatment effect if one is present  
329 – by decreasing variability that is unrelated to the study drug [6]. One strategy is to identify  
330 and select patients who are likely to adhere to treatment, but only prior to randomisation,  
331 not afterwards. Otherwise, this step could impact the statistical validity and conclusions of  
332 the trial: indeed, adherence alone, even to placebo, has been linked to better outcomes in a  
333 trial. In addition, a protocol that is partially masked to participants and investigators during a  
334 run-in period can reduce the risk that adherence may be overly and artificially encouraged.

335 Other measures discussed include making patients aware of the conditions and demands of  
336 the trial, avoiding overly rapid initial titrations to reduce initial side effects, and using  
337 adherence prompts and feedback, for example, using dosing history data from smart bottles  
338 to encourage good adherence. These strategies can also be used in safety assessments [6].

339 It is also advisable to consider complexity and stringency when designing a trial protocol to  
340 facilitate adherence [36].

341 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is an  
342 international initiative that aims to improve the quality of clinical trial protocols, by defining  
343 an evidence-based set of items that should be included in a clinical trial protocol [40, 41]. One  
344 component of this is a section on adherence, which provides guidance on procedures and  
345 strategies for monitoring and improving adherence and reporting this clearly in the study  
346 protocol.

347 Adherence interventions in a trial setting mainly fall into two categories: 1) approaches to  
348 identify adherence issues in the trial preparation and run-in phases; and 2) approaches to  
349 directly improve adherence to the trial protocol and/or the investigational drug.

350

## 351 **[Heading 2] Trial preparation and run-in phases**

352 Previous participation in another trial, within a specific time period, is a common criterion for  
353 participant exclusion. However, some participants have been shown to mislead investigators  
354 about this point [29]. One solution is to use participant registries, and this precaution may  
355 reduce the risk of enrolling participants who are involved in multiple trials [36]. In some  
356 markets, including France and the United Kingdom, registration of Phase I volunteers is  
357 mandatory. It is increasingly apparent that this requirement is needed for Phase II – IV trials.

358

359 Some pharmaceutical sponsors use participant identifiers to identify duplicate enrollers in  
360 their own trials. However, these techniques do not identify them across sponsors. There are  
361 also various systems, including Verified Clinical Trials, CTSdatabase and Dupcheck, which use  
362 GDPR and HIPPA compliant databases to identify duplicate enrollers and thus verify eligibility  
363 [36].

364

365 Shiovitz et al. (2016) recommend sharing only limited inclusion and exclusion criteria during  
366 recruitment, to ensure participants do not have the information they would need to feign  
367 inclusion characteristics. Other recommendations include ensuring stipends are reasonable,

368 to discourage “professional” subjects and reduce the risk of coercing participation, and  
369 requiring site investigators to enrol at least half of participants from internal databases that  
370 offer a known source of eligible participants. The authors further recommend that  
371 investigators should be reimbursed appropriately in terms of screen-fail ratios, as a low  
372 screen-fail ratio may encourage investigators to screen in ineligible participants in order to  
373 secure payment [36].

374

375 As discussed above, the use of single-blind placebo run-in periods with adherence monitoring  
376 has been recommended, to identify participants who are inclined to respond to placebo, and  
377 those inclined to be non-adherent to the investigational drug and/or protocol requirements  
378 [6, 29]. These participants can thus be excluded according to predefined criteria or accounted  
379 for in the analysis of the trial. As noted in the FDA guidance, it is important that identification  
380 is done before randomisation [6].

381

382 The FDA guidance describes the run-in period approach as an enrichment strategy that has  
383 the potential to decrease heterogeneity (non-drug related variability) and thus increase study  
384 power to detect a real drug effect [6]. However, investigators must carefully consider exactly  
385 how to analyse data from participants who, during the run-in period, have been identified as  
386 placebo responders or low adherers. This decision must be guided by the objective of the  
387 study [3]. It may not always be appropriate to simply exclude these participants. Instead, the  
388 information may be used to inform the analysis of sub-populations.

389

390 Despite recommending them, the FDA guidance recognises that enrichment strategies may  
391 limit the generalisability and applicability of the study results. [6] Therefore, care should be  
392 taken to ensure that sufficient data are collected on the full range of individuals who may  
393 later receive the drug post-approval.

394

395 **[Heading 2] Approaches to directly improve adherence**

396 The FDA guidance also describes a range of methods that can be used to positively affect  
397 adherence [6]. However, the ethics of directly encouraging ingestion of an investigational  
398 drug need to be carefully considered, in particular before efficacy and safety have been  
399 established, as a trial participant must remain free to discontinue treatment without  
400 explanation and prejudice, and must also feel free to report any adverse reactions or  
401 experiences of taking the drug [29]. FDA guidance recommends adherence feedback at the  
402 point of care to avoid this ethical issue. To avoid potential source of bias, it is recommended  
403 to provide standard adherence monitoring and support to all participants in both active and  
404 placebo arms.

405

406 McCann et al. (2016) recommend financial incentives, not to increase adherence but rather,  
407 to encourage participants to report adherence accurately, whether the drug has been taken  
408 or not [29]. However, this approach carries the risk of biasing a participant's response,  
409 because they are incentivised to give a response at each point of measurement.

410

411 One strategy that has great potential is patient-centred trial design. It can encourage  
412 adherence not only to the requirements of the study period but also throughout follow-up,  
413 which is often lengthy. This approach includes steps such as: seeking patient input at the  
414 design stage, to ensure patient-friendly study materials and processes are used to help  
415 explain and implement the clinical trial; choosing outcomes that are meaningful to patients;  
416 and minimising participant burden from clinic visits via greater use of at-home electronic data  
417 capture. [42]

418

419 **[Heading 1] Analysing and interpreting adherence data in clinical trials**

420 This section links to items 5 – 8 in the EMERGE guideline, which describe the trial design and  
421 statistical analysis elements that should be considered a priori and reported at the end of the  
422 trial [5].

423

424 Non-adherence to a planned treatment regimen in placebo-controlled trials can diminish the  
425 causal treatment effect (i.e. efficacy) and make a treatment look less effective than it really is  
426 [36, 43, 44]. This causes many problems, some of which have been discussed above.

427

428 In placebo-controlled trial analysis, non-adherence fundamentally alters what is meant by the  
429 ‘treatment effect’. If non-adherence is ignored in the statistical analysis, the true efficacy of  
430 treatment will be diminished, resulting in overly conservative estimates of efficacy. In  
431 contrast, in safety analyses and in analyses of non-inferiority and equivalence trials, the  
432 diminishing effect of non-adherence is usually anti-conservative, which means a harmful  
433 treatment is more likely to be accepted as harmless and equivalency or non-inferiority are  
434 more likely to be declared [44,45]. There is also some evidence that patterns and causes of  
435 non-adherence can influence the treatment effect in different ways, making it difficult to  
436 predict the overall effect [46,47].

437

438 A recent review found that a majority of trials are subject to various forms of non-adherence  
439 to the treatment protocol, and investigators attempt to deal with non-adherence using a  
440 variety of statistical methods and analysis populations. However, they rarely consider the  
441 potential for the introduction of bias [45]. Here, we present recent research and  
442 recommendations on how to account for non-adherence in trial analyses, to better estimate  
443 treatment efficacy.

444

## 445 **[Heading 2] Planned approaches**

446 If non-adherence is foreseeable in a trial, investigators should plan for this at the design  
447 stage, both to demonstrate transparency and to ensure all data that will be necessary for  
448 analysis are collected. Dodd et al. (2017) have published a useful set of recommendations to  
449 enable adequate data collection [43]. For analysis, current draft International Conference on  
450 Harmonisation (ICH) guidelines (E9(R1) 2017) state that clear trial objectives should be



451 translated into key scientific questions of interest, and suitable estimands (the target of  
452 estimation for these questions, see box) chosen to address them, before an appropriate  
453 statistical analysis plan is specified. EMERGE sections 7 and 8 can guide the selection of an  
454 estimand by helping to define the parameters of non-adherence [5] After the estimands are  
455 settled, an appropriate statistical analysis can be specified [7].

456

### 457 **[Heading 3] Intention-to-treat**

458 It is generally recommended to perform the primary efficacy analysis under the intention-to-  
459 treat (ITT) principle [43], where all participants are included in the analysis and treatments  
460 are compared between randomised arms, regardless of which treatment the participants  
461 actually received. This preserves the element of randomisation, ensuring that no baseline  
462 confounding is expected to affect the analysis. Current ICH guidelines describe five ITT  
463 strategies, each for different estimands of subtly different treatment effects of interest [7].  
464 The first is treatment policy, which is the strategy most commonly associated with ITT  
465 analyses and the one prone to underestimating efficacy. This estimand is useful in pragmatic  
466 trials that are looking for the population effect of implementing a treatment policy, with real-  
467 world deviations from the protocol taken into account.

468

### 469 **[Heading 3] Additional strategies**

470 However, when interest lies in more precisely estimating efficacy, and appropriate data on  
471 adherence are available, the remaining four strategies can be employed in addition to (or  
472 instead of, depending on the aims of the trial) the treatment policy strategy. Briefly, these  
473 are:

- 474 1. **The composite strategy**, where non-adherence is integrated into the (adverse)  
475 outcome of interest. With this strategy we assume non-adherence adds meaningful  
476 information about the overall effect of the treatment. As an example, perhaps  
477 participants did not adhere to the treatment because they could not tolerate it, or  
478 they experienced other adverse events that had an influence on the treatment effect.  
479 The outcome would be expanded to include either the event under study, or failure  
480 to adhere to or withdrawal from treatment, and randomised groups would be  
481 compared in an appropriate statistical analysis.

482 2. **The hypothetical strategy**, where the treatment effect is that which would have been  
483 seen if everyone had adhered perfectly to treatment through the end of follow-up.  
484 Strong assumptions are required for this effect to be meaningful, including that  
485 medication non-adherence was unrelated to tolerability (see ICH E9 (R1) guidelines  
486 for further discussion). In this strategy, outcome measurements that were not  
487 observed due to non-adherence can be imputed under plausible missingness  
488 assumptions, and an appropriate statistical analysis can be performed on the imputed  
489 dataset(s).

490 3. **The principle stratum strategy**, where the treatment effect is that which would be  
491 seen in the stratum of people who 1) would be able to perfectly adhere to either  
492 treatment, and 2) would actually do so. This subset of randomised participants cannot  
493 be directly known because valid reasons for non-adherence (such as medication  
494 intolerability) cannot be predicted in advance, and they cannot be inferred after the  
495 trial has been completed as participants can only receive one treatment. However,  
496 investigators can attempt to infer membership in this stratum from covariates and  
497 perform the statistical analysis on data from these participants only. At the design  
498 stage investigators may also consider specifying markers of good adherence and  
499 restricting participation with relevant inclusion or exclusion criteria and/or they may  
500 consider using special trial designs such as run-in, enrichment or randomised  
501 withdrawal, though these strategies may decrease the generalisability of the results.

502 4. **The while on treatment strategy**, where the treatment effect is a weighted average  
503 of the outcomes seen while adhering to treatment (rather than the effect seen by a  
504 pre-specified time point). An appropriate statistical analysis that accounts for time in  
505 adherence can then be performed.

506 Which one to use will depend on the estimand of interest. Since all of these strategies are  
507 underpinned by assumptions, it is best to use one or more sensitivity analyses to test them.  
508 For a thorough discussion, see the ICH Harmonised Guideline for Estimands and Sensitivity  
509 Analyses in Clinical Trials [7].

510

511 **[Heading 2] Less preferable strategies**

512 Other analysis principles, such as per-protocol (PP) and as-treated (AT) analyses, attempt to  
513 address questions of adherence and efficacy. However, they are not usually suitable. PP  
514 analyses typically exclude or censor participants who deviate from the treatment protocol,  
515 before comparing treatments between randomised arms. However, because the treatment  
516 protocols are likely to present different challenges to adherence, the participant groups may  
517 not be comparable [44]. AT analyses include all participants, but analyse them according to  
518 the treatment they actually received, discarding randomisation. Both of these analyses are  
519 prone to selection bias, so confounding must be considered and appropriately adjusted for in  
520 statistical analysis. As it is usually not possible to completely adjust for all possible sources of  
521 confounding, neither of these is preferable to an appropriately designed ITT analysis.

522

## 523 **[Heading 2] Unplanned approaches**

524 If non-adherence was not considered during trial design (so no planned analyses incorporate  
525 it), but relevant data are available for analysis, investigators may decide to perform one of  
526 the above analyses post-hoc. However, care must still be taken in selecting an appropriate  
527 estimand and, as with all post-hoc investigations, investigators must use caution and avoid  
528 over-interpreting results from unplanned analyses.

529

530 More advanced statistical techniques can also estimate causal treatment effects and account  
531 for non-adherence to treatment, while maintaining the balance produced by randomisation.  
532 Some examples include randomisation-based efficacy estimation [48] instrumental variable  
533 [49], and complier average causal effect (CACE) [50] methods. Such analysis techniques are  
534 not yet commonly used, as they tend to be more complex and/or computationally intensive  
535 than the previously discussed analyses. They also rely on potentially unverifiable  
536 assumptions, which are often stronger than those required for ITT analyses. However, this  
537 area of research is growing and some [35] are calling for increased awareness and uptake of  
538 these methods.

539

540 Although it may be possible to estimate causal treatment effects after a trial has started, or  
541 even after it has ended, pre-planned statistical analyses always give weightier and more

542 transparent results than post-hoc analyses. Therefore, identifying potential adherence issues  
543 early in the clinical trial programme is crucial.

544

## 545 **[Heading 2] Safety analyses**

546 Although much research has gone into methods of accounting for non-adherence in  
547 estimating treatment efficacy, there is to our knowledge no research and guidance on the  
548 appropriate analysis population to use for harms outcomes in the presence of such  
549 nonadherence [45]. This is likely due to a more widespread lack of good practice around  
550 collecting, reporting and analysing harms in clinical trials. A recent systematic review [51] of  
551 trial results reported in four high-impact journals found that these items were inconsistently  
552 undertaken and concluded that statistical analysis, in particular, was often deemed  
553 inappropriate and suboptimal, potentially leading to missed harm signals and unsafe  
554 treatments being declared safe. In addition, because adverse events are unpredictable in  
555 advance, safety analyses are not often well-powered. The problem of low power is  
556 exacerbated by non-adherence, which could preclude the observation of adverse events that  
557 would otherwise have occurred; further, non-adherence could itself be a consequence of side  
558 effects that were on the path towards an adverse event. More research is needed on how to  
559 deal with non-adherence in safety analyses.

560

## 561 **[Heading 1] Reporting adherence data from clinical trials**

562 The EMERGE guidelines [5] should be used in harmony with reporting guidelines for clinical  
563 trials, such as STROBE [9] and CONSORT, [8] to ensure that all the relevant aspects of the  
564 adherence data are reported in a relevant and appropriate manner. The minimum reporting  
565 criteria include: 1) the phases of adherence being studied; 2) the operational definition of  
566 each adherence phase; 3) the measurement method/s used; and 4) the results of the analysis  
567 appropriate for each phase being studied [5].

568

569 [SUGGESTED CALL OUT BOX TEXT]

570 An estimand is simply a treatment effect 'of interest' for a clinical question. The treatment  
571 effect in a perfect setting, where 100% of trial participants would adhere to their treatment  
572 throughout the entire follow-up period, is a pure effect of the treatment. It is how the

573 outcome of treatment, taken exactly as prescribed, compares to what would have happened  
574 to the same subjects had they all taken the alternative (or no) treatment exactly as prescribed.  
575 Often this is the effect ‘of interest’; however, non-adherence reduces or increases the amount  
576 of exposure to the treatment and muddles this interpretation. In this situation there are  
577 several possible ‘treatment effects’ that could be obtained, each answering slightly different  
578 questions.

579

580 The EMERGE guideline highlights the information required to define an estimand for a clinical  
581 trial that factors adherence into the treatment effect. Estimands have four elements [7]:

- 582 1. the target population (e.g. the stratum of participants who *would* adhere to treatment  
583 if they could tolerate it: EMERGE items 5a-5c elicit information to help define this [5])
- 584 2. the variable or endpoint to be obtained for each participant (e.g. treatment failure  
585 defined as non-response *or* treatment discontinuation: EMERGE item 6a [5])
- 586 3. the specification of how to account for non-adherence and other treatment-altering  
587 events (see text for a description of potential strategies: EMERGE items 7a-b[5])
- 588 4. the population-level summary for the variable, which can be compared between  
589 treatment conditions (e.g. mean change in outcome or proportion of treatment  
590 failures: EMERGE items 8a-b, 9a-b [5]).

591

592 [END OF BOX TEXT]

593

## 594 **[Heading 1] Conclusions**

595 Unidentified non-adherence in clinical trial settings is a substantial and costly challenge that  
596 directly or indirectly affects all stakeholders. Non-adherence in clinical trials can obscure  
597 exposure-response estimations and confound safety and efficacy signals. Addressing this  
598 issue offers benefits to all. For drug developers, it is likely to be more cost-effective to identify  
599 and manage non-informative data or use trial enrichment strategies to increase study power,  
600 than to manage the effect of non-adherence by increasing sample size [36]. Patients stand to  
601 benefit from safer and more effective dosing regimens, which have been established based  
602 on adherence-informed results [3]. The EMERGE guideline [5] can help drug developers and  
603 researchers to better understand how adherence data should be collected, analysed, and  
604 reported in clinical trial settings, and can be used to drive improvement in addressing the

605 pervasive issue of non-adherence in clinical trials. To align with previously published guidance  
606 specifying that adherence to investigational products and trial protocols should be adequately  
607 reported [6,7], pharmaceutical regulators need to officially endorse EMERGE [5] to drive  
608 positive change, and ensure clinical trial sponsors and research organisations can achieve  
609 appropriate alignment with these guidelines.

610

#### 611 **Conflict of interest statement**

612 The authors declare the following conflicts of interest: LLE and CAJ are owners and directors  
613 of Sprout Behaviour Change Ltd. Bernard Vrijens owns shares and is a director at AARDEX  
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616

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628

629

630 **References**

- 631 1. Gossec L, Tubach F, Dougados M, Ravaud P. Reporting of adherence to medication in  
632 recent randomized controlled trials of 6 chronic diseases: a systematic literature  
633 review. *Am J Med Sci.* 2007;334(4):248-254.
- 634 2. Kastrissios H, Blaschke TF. Medication compliance as a feature in drug development.  
635 *Annu Rev Pharmacol Toxicol.* 1997;37:451-475.
- 636 3. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for  
637 medication adherence in clinical trials. *Clin Pharmacol Ther.* 2014;95(6):617-626.
- 638 4. Valgimigli M, Garcia Garcia HM, Vrijens B, et al. Standardized classification and  
639 framework for reporting, interpreting, and analysing medication non-adherence in  
640 cardiovascular clinical trials: a consensus report from the Non-adherence Academic  
641 Research Consortium (NARC). *Eur Heart J.* 2018;ehy377.
- 642 5. De Geest S, Zullig LL, Dunbar-Jacob J, et al. ESPACOMP Medication Adherence  
643 Reporting Guideline (EMERGE). *Ann Intern Med.* 2018;169(1):30-35.
- 644 6. US Food and Drug Administration. Enrichment Strategies for Clinical Trials to Support  
645 Approval of Human Drugs and Biological Products: Guidance for Industry. Final. FDA;  
646 March 2019. [https://www.fda.gov/regulatory-information/search-fda-guidance-  
647 documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-  
648 biological-products](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products) Accessed 19 November 2019.
- 649 7. European Medicines Agency. *ICH E9 (R1) Addendum on Estimands and Sensitivity*  
650 *Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials*  
651 *Step 2b.*EMA: 2017. [https://www.ema.europa.eu/en/documents/scientific-  
652 guideline/draft-ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-  
653 guideline-statistical\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical_en.pdf) Accessed 19 November 2019.
- 654 8. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration:  
655 updated guidelines for reporting parallel group randomised trials. *BMJ.*  
656 2010;340:c869.
- 657 9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of  
658 Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting  
659 observational studies. *Lancet.* 2007;370(9596):1453-1457.
- 660 10. Enhancing the QUALity and Transparency Of health Research. How to develop a  
661 reporting guideline. Equator Network: 2018. [http://www.equator-  
662 network.org/toolkits/developing-a-reporting-guideline/](http://www.equator-network.org/toolkits/developing-a-reporting-guideline/) Accessed 19 November  
663 2019.
- 664 11. European Medicines Agency. *ICH E3 Structure and Content of Clinical Study Reports*  
665 *(CPMP/ICH/137/95).* EMA;  
666 1996. [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-  
667 structure-content-clinical-study-reports-step-5\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step-5_en.pdf) Accessed 19 November 2019.
- 668 12. National Institute for Health and Clinical Excellence. *Medicines Adherence: Involving*  
669 *Patients in Decisions About Prescribed Medicines and Supporting Adherence.*  
670 London: NICE; 2009. <https://www.nice.org.uk/guidance/cg76> Accessed 19  
671 November 2019.
- 672 13. Khan R, Socha-Dietrich K. Investing in Medication Adherence Improves Health  
673 Outcomes and Health System Efficiency. DELSA/HEA/WD/HWP(2018)2. Organisation  
674 for Economic Co-operation and Development.; 2018.  
675 [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DELSA/H  
676 EA/WD/HWP\(2018\)2&docLanguage=En](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DELSA/HEA/WD/HWP(2018)2&docLanguage=En) Accessed 19 November 2019.

- 677 14. World Health Organization. Adherence to Long-term Therapies: Evidence for Action.  
678 Switzerland: WHO;2003.  
679 [https://www.who.int/chp/knowledge/publications/adherence\\_report/en/](https://www.who.int/chp/knowledge/publications/adherence_report/en/) Accessed  
680 19 November 2019.
- 681 15. Elliott R. Non-adherence to medicines: not solved but solvable. *J Health Serv Res*  
682 *Policy*. 2009;14(1):58-61.
- 683 16. Trueman P, Lawson K, Blighe A. Evaluation of the Scale, Causes and Costs of Waste  
684 Medicines: Final Report. York Health Economics Consortium; School of Pharmacy,  
685 University of London;2010.  
686 [https://discovery.ucl.ac.uk/id/eprint/1350234/1/Evaluation\\_of\\_NHS\\_Medicines\\_Wa](https://discovery.ucl.ac.uk/id/eprint/1350234/1/Evaluation_of_NHS_Medicines_Waste_web_publication_version.pdf)  
687 [ste\\_web\\_publication\\_version.pdf](https://discovery.ucl.ac.uk/id/eprint/1350234/1/Evaluation_of_NHS_Medicines_Waste_web_publication_version.pdf) Accessed 19 November 2019.
- 688 17. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights  
689 arising from studies on the unreliable link between prescribed and actual drug  
690 dosing histories. *Annu Rev Pharmacol Toxicol*. 2012;52:275-301.
- 691 18. Murali KM, Mullan J, Chen JH, Roodenrys S, Lonergan M. Medication adherence in  
692 randomized controlled trials evaluating cardiovascular or mortality outcomes in  
693 dialysis patients: A systematic review. *BMC Nephrol*. 2017;18(1):42.
- 694 19. Corneli AL, Deese J, Wang M, et al. FEM-PrEP: adherence patterns and factors  
695 associated with adherence to a daily oral study product for pre-exposure  
696 prophylaxis. *J Acquir Immune Defic Syndr*. 2014;66(3):324-331.
- 697 20. Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance,  
698 compliance, and compliance. *Mol Interv*. 2011;11(2):107-110.
- 699 21. Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor  
700 medication adherence in clinical trials: consequences and solutions. *Nat Rev Drug*  
701 *Discovery*. 2017;16(3):149-150.
- 702 22. Mallayasamy S, Chaturvedula A, Blaschke T, Fossler MJ. A systematic evaluation of  
703 effect of adherence patterns on the sample size and power of a clinical study. *CPT*  
704 *Pharmacometrics Syst Pharmacol*. 2018;7(12):818-828.
- 705 23. Fossler MJ Patient adherence: clinical pharmacology's embarrassing relative. *J Clin*  
706 *Pharmacol*. 2015;55(4):365-367.
- 707 24. Cross J, Lee H, Westelinck A, Nelson J, Grudzinskas C, Peck C. Postmarketing drug  
708 dosage changes of 499 FDA-approved new molecular entities, 1980-1999.  
709 *Pharmacoepidemiol Drug Saf*. 2002;11(6):439-446.
- 710 25. Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after  
711 market introduction. *Pharmacoepidemiol Drug Saf*. 2002;11(6):447-453.
- 712 26. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry:  
713 New estimates of R&D costs. *J Health Econ*. 2016;47:20-33.
- 714 27. Smith DL. Patient nonadherence in clinical trials: Could there be a link to  
715 postmarketing patient safety? *Drug Inf J*. 2012;46(1):27-34.
- 716 28. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining  
717 adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.
- 718 29. McCann DJ, Petry NM, Bresell A, Isacson E, Wilson E, Alexander RC. Medication  
719 nonadherence, professional subjects, and apparent placebo responders: Overlapping  
720 challenges for medications development. *J Clin Psychopharmacol*. 2015;35(5):566-  
721 573.
- 722 30. Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to  
723 measure treatment adherence. *Med Pharm Rep*. 2019;92(2):117-122.



- 724 31. Lam WY, Fresco P. Medication adherence measures: An overview. *Biomed Res Int*.  
725 2015;217047.
- 726 32. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales  
727 really measuring? A systematic review. *Br J Clin Pharmacol*. 2014;77(3):427-445.
- 728 33. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-  
729 reported medication adherence for routine clinical use: a systematic review. *BMC*  
730 *Med Res Methodol*. 2011;11:149.
- 731 34. Nunn A, Anywaive Z, Seeley J, et al. Exit interviews administered to patients  
732 participating in the COSTOP placebo controlled randomised trial in Uganda. *Contemp*  
733 *Clin Trials Commun*. 2016;3:142-146.
- 734 35. Podsadecki TJ, Vrijens BC, Tousset EP, Rode RA, Hanna GJ. "White coat compliance"  
735 limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. *HIV*  
736 *Clin Trials*. 2008;9(4):238-246.
- 737 36. Shiovitz TM, Bain EE, McCann DJ, et al. Mitigating the effects of nonadherence in  
738 clinical trials. *J Clin Pharmacol*. 2016;56(9):1151-1164.
- 739 37. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is  
740 medication taken as prescribed? A novel assessment technique. *JAMA*.  
741 1989;261(22):3273-3277.
- 742 38. US Food and Drug Administration. K113070 De Novo Summary – Proteus.  
743 FDA; 2012. [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/K113070.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf)  
744 Accessed 19 November 2019.
- 745 39. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system  
746 for monitoring adherence to tuberculosis therapy. *PLoS ONE* 2013;8(1):e53373.
- 747 40. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard  
748 protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.
- 749 41. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration:  
750 guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
- 751 42. Mullins CD, Vandigo J, Zheng Z, Wicks P. 2014. Patient-centeredness in the design of  
752 clinical trials. *Value in Health*. 2014;17(4); 471-475.
- 753 43. Dodd S, White IR, Williamson P. A framework for the design, conduct and  
754 interpretation of randomised controlled trials in the presence of treatment changes.  
755 *Trials*. 2017;18(1):498.
- 756 44. International Council for Harmonisation. ICH harmonised tripartite guideline.  
757 Statistical principles for clinical trials. International Conference on Harmonisation E9  
758 Expert Working Group. *Stat Med*. 1999;18(15):1905-1942.
- 759 45. Dodd S, White IR, Williamson P. Nonadherence to treatment protocol in published  
760 randomised controlled trials: a review. *Trials*. 2012;13:84.
- 761 46. Sheng D, Kim MY. The effects of non-compliance on intent-to-treat analysis of  
762 equivalence trials. *Stat Med*. 2006;25(7):1183-1199.
- 763 47. Wangge G, Klungel OH, Roes KC, de Boer A, Hoes AW, Knol MJ. Room for  
764 improvement in conducting and reporting non-inferiority randomized controlled  
765 trials on drugs: a systematic review. *PLoS One*. 2010;5(10):e13550.
- 766 48. White IR. Uses and limitations of randomization-based efficacy estimators. *Stat*  
767 *Methods Med Res*. 2005;14(4):327-347.
- 768 49. Dunn G, Maracy M, Tomenson B. Estimating treatment effects from randomized  
769 clinical trials with noncompliance and loss to follow-up: the role of instrumental  
770 variable methods. *Stat Methods Med Res*. 2005;14(4):369-395.

- 771 50. Little RJ, Yau LH. Statistical techniques for analyzing data from prevention trials:  
 772 Treatment of no-shows using Rubin's causal model. *Psychological Methods*.  
 773 1998;3(2):147-159.
- 774 51. Phillips R, Hazell L, Sauzet O, et al. Analysis and reporting of adverse events in  
 775 randomised controlled trials: a review. *BMJ Open* 2019;9:e024537.

776  
 777 Table 1. Potential adherence measures to assess initiation, implementation, and/or  
 778 persistence, as well as reasons for non-adherence

Adherence measure	Initiation date	Implementation	Discontinuation date	Reasons for non adherence
Directly observed therapy	✓ ✓	✓ ✓ (Full dosing history)	✓ ✓	X
Pill count	X	✓ (Only aggregate dosing summary) Subject to social desirability bias	X	X
Patient-reported outcome measures (self-reported adherence)	✓ Subject to desirability bias	✓ Subject to recall bias	✓ Subject to desirability bias	✓ ✓ In particular when combined with a sound measure of adherence
Drug or drug-metabolite monitoring	X	✓ Sparse data and subject to white coat adherence bias	X	X
Electronic detection of package entry	✓ ✓ Requires activation at patient initiation in the trial	✓ ✓ (Full dosing history)	✓ ✓	X
Ingestible sensor e.g. breathalysers smart pill	✓ ✓ Requires activation at patient initiation in the trial	✓ ✓ (Full dosing history) Perceived intrusiveness and directions for using sensor should be considered	✓ ✓	X
Pharmacy claims and refill data	✓ (Date of first fill may differ from formal treatment initiation)	✓ (Only an aggregate dosing summary)	✓ (Not precise, typically 90 days uncertainty)	X

779 ✓ =suitable, ✓ ✓ =very suitable, X = not suitable

780  
 781

782 **Figure legends**

783 *Figure 1. Illustration of the process of medication adherence according to the ABC Taxonomy*  
784 *[28] adapted to a clinical trial setting. The example is illustrating a twice a day dosing*  
785 *schedule.*