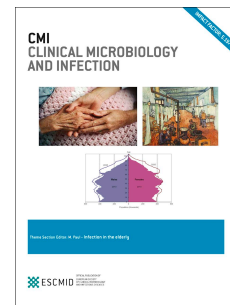


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Optimising design of research to evaluate antibiotic stewardship interventions;
consensus recommendations of a multinational working group

Valentijn A. Schweitzer, Cornelis H. van Werkhoven, Jesús Rodríguez Baño, Julia Bielicki, Stephan Harbarth, Marlies Hulscher, Benedikt Huttner, Jasmin Islam, Paul Little, Celine Pulcini, Alessia Savoldi, Evelina Tacconelli, Jean-Francois Timsit, Maarten van Smeden, Martin Wolkewitz, Marc J.M. Bonten, A. Sarah Walker, Martin J. Llewelyn, Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working Group on Design of Antimicrobial Stewardship Evaluations



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1 **Optimising design of research to evaluate antibiotic stewardship interventions; consensus**
2 **recommendations of a multinational working group.**

3

4 Valentijn A. Schweitzer¹, Cornelis H. van Werkhoven¹, Jesús Rodríguez Baño², Julia Bielicki³,
5 Stephan Harbarth⁴, Marlies Hulscher⁵, Benedikt Huttner⁶, Jasmin Islam⁷, Paul Little⁸, Celine
6 Pulcini⁹, Alessia Savoldi^{10,11}, Evelina Tacconelli^{10,11}, Jean-Francois Timsit¹², Maarten van
7 Smeden¹³, Martin Wolkewitz¹⁴, Marc J.M. Bonten¹⁵, A. Sarah Walker^{16,17}, and Martin J.
8 Llewelyn⁷, Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working
9 Group on Design of Antimicrobial Stewardship Evaluations.

10

11 *1. Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, The*
12 *Netherlands*

13 *2. Unit of Infectious Diseases, Clinical Microbiology and Preventive Medicine, Department of*
14 *Medicine, Hospital Universitario Virgen Macarena, Universidad de Sevilla and Biomedicine*
15 *Institute of Sevilla (IBiS), Seville, Spain*

16 *3 Paediatric Infectious Disease Research Group, St George's University of London, London,*
17 *United Kingdom*

18 *4. Divisions of Infectious Diseases and Infection Control, Geneva University Hospitals and*
19 *Faculty of Medicine, Switzerland*

20 *5. Scientific Center for Quality of Healthcare, Radboud Institute for Health Sciences, Radboud*
21 *University Medical Center, Nijmegen, The Netherlands.*

22 *6. Department of Infectious Diseases and Infection Control, Hôpitaux Universitaires de*
23 *Genève, Switzerland*

- 24 7. Department of Global Health and Infection, Brighton and Sussex Medical School, Falmer,
25 United Kingdom
- 26 8. Department of Primary Care Research, University of Southampton, Southampton, United
27 Kingdom
- 28 9. Infectious Diseases Department, Université de Lorraine, CHRU-Nancy, and APEMAC,
29 Université de Lorraine, Nancy, France.
- 30 10. Infectious Diseases, Department of Diagnostic and Public Health, Verona, Italy
- 31 11. University Hospital; Internal Medicine, Tuebingen University, Germany.
- 32 12. University of Paris, IAME ; Inserm; Medical and Infectious diseases ICU (MI2), Bichat
33 hospital; F75018 , Paris France.
- 34 13. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The
35 Netherlands.
- 36 14. Institute for Medical Biometry and Statistics, University of Freiburg, Germany
- 37 15. Department of Medical Microbiology, University Medical Center Utrecht, The
38 Netherlands
- 39 16. MRC Clinical Trials Unit, University College London, London, United Kingdom
- 40 17. Nuffield Department of Medicine, University of Oxford, United Kingdom

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42

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47 **Corresponding author:**

48 Martin J Llewelyn

49 Department of Global Health and Infection

50 Brighton and Sussex Medical School

51 University of Sussex

52 Falmer, East Sussex. BN1 9PS

53 United Kingdom

54 m.j.llewelyn@bsms.ac.uk

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55 Abstract**56 Scope**

57 Antimicrobial stewardship interventions and programmes aim to ensure effective treatment
58 while minimising antimicrobial-associated harms including resistance. Practice in this vital
59 area is undermined by the poor quality of research addressing both what specific
60 antimicrobial use interventions are effective and how antimicrobial use improvement
61 strategies can be implemented into practice. In 2016 we established a working party to
62 identify the key design features which limit translation of existing research into practice and
63 then to make recommendations for how future studies in this field should be optimally
64 designed. The first part of this work has been published as a systematic review. Here we
65 present the working group's final recommendations.

66 Methods

67 An international working group for design of antimicrobial stewardship intervention
68 evaluations was convened in response to the fourth call for leading expert network
69 proposals by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). The
70 group comprised clinical and academic specialists in antimicrobial stewardship and clinical
71 trial design from six European countries. Group members completed a structured
72 questionnaire to establish the scope of work and key issues to develop ahead of a first face-
73 to-face meeting which 1) identified the need for a comprehensive systematic review of
74 study designs in the literature and 2) prioritised key areas where research design
75 considerations restrict translation of findings into practice. The working group's initial
76 outputs were reviewed by independent advisors and additional expertise was sought in
77 specific clinical areas. At a second face-to-face meeting the working group developed a

78 theoretical framework and specific recommendations to support optimal study design.
79 These were finalised by the working group co-ordinators and agreed by all working group
80 members

81 **Recommendations**

82 We propose a theoretical framework in which consideration of the **intervention rationale**
83 the **intervention setting, intervention features** and the **intervention aims** inform selection
84 and prioritization of outcome measures, whether the research sets out to determine
85 **superiority** or **non-inferiority** of the intervention measured by its primary outcome(s), the
86 most appropriate **study design** (e.g. experimental or quasi- experimental) and the **detailed**
87 **design features**. We make eighteen specific recommendation in three domains: outcomes,
88 objectives and study design.

89 **Conclusions**

90 Researchers, funders and practitioners will be able to draw on our recommendations to
91 most efficiently evaluate antimicrobial stewardship interventions.

92

93

94 **Background and context**

95 Antimicrobial resistance is a rapidly growing and major threat to human health (1). Overuse
96 of antimicrobials drives resistance at the individual (2) and population level (3). The term
97 antimicrobial stewardship refers to interventions and programmes which aim to optimise
98 antimicrobial use; achieving effective treatment while minimising antimicrobial-associated
99 harms including resistance (4).

100 Despite the large and exponentially increasing number of studies published since the term
101 Antimicrobial Stewardship was coined (5-7), evidence remains remarkably weak both for
102 **what** specific antimicrobial use interventions are effective (in terms of mortality, length of
103 stay, adverse events, resistance rates) and **how** antimicrobial use improvement strategies
104 can be implemented to deliver the desired antimicrobial use in daily clinical practice (8). A
105 2016 systematic review of evidence supporting key antimicrobial use interventions (e.g.
106 prescribing according to guidelines, de-escalation of therapy, intravenous to oral switching)
107 identified predominantly low-quality and highly heterogenous supporting evidence (9). The
108 evidence around improvement strategies is similarly weak, dominated by uncontrolled
109 before-after studies and inadequately performed interrupted time series analyses, mostly
110 performed within single hospitals (10).

111 We recently reported a broad systematic review of antimicrobial stewardship intervention
112 studies which highlighted key frequent design weaknesses (7). Studies which aim to assess
113 effectiveness of antimicrobial use interventions are typically under powered and fail to
114 provide evidence on safety or even do not report clinical outcome data at all. Improvement
115 strategy studies are often multifaceted with inadequate process evaluation to allow
116 mediators of impact to be assessed (11). Generally, the field of antimicrobial stewardship

117 research is dominated by single-centre observational and quasi-experimental studies which
118 fail to deal optimally with risks of different forms of bias and that lack external validity (7, 8).
119 Building on this work we established a working group of investigators in this field which
120 used a consensus-building iterative process over 12 months to build a conceptual
121 framework and develop specific recommendations for the design of stewardship
122 evaluations, which were then reviewed and amended by an expert advisory committee. This
123 guidance is the final result of that process and aims to support investigators when making
124 key design decisions and funders assessing proposals for studies of antimicrobial
125 stewardship interventions and hopefully enhances the quality and impact of research in this
126 crucial area.

127 **Methods**

128 An international working group for design of antimicrobial stewardship intervention
129 evaluations was convened in response to the fourth call for leading expert network
130 proposals by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). The
131 study sponsor was the UK Medical Research Council. The working group co-ordinators
132 (MJMB, MJL) and co-applicants (VAS, ASW and CHvW) purposively selected an additional
133 eight leading clinical and academic specialists in antimicrobial stewardship and clinical trial
134 design from six European countries (France, Germany, Italy, the Netherlands, Spain,
135 Switzerland and the UK) to contribute. Selection secured input from the diversity of
136 professionals involved in antimicrobial stewardship practice (infection, internal medicine,
137 intensive care medicine) and research (trial design, statistics and qualitative research)
138 disciplines. Consensus was sought through a nominal group process. Group members
139 completed a structured questionnaire to establish the scope of work, key study designs

140 used in antimicrobial stewardship, identify the major limitations on different study designs
141 and key issues to develop ahead of a first face-to-face meeting. The group met in March
142 2017 and anonymised responses were feedback to the whole group and relevant literature
143 was presented (VAS, CHvW, MJL). This identified the need for a comprehensive systematic
144 review of study designs in the literature. In parallel, in moderated small group work,
145 candidate solutions were proposed to address the limitations identified, and in a final
146 round-table moderated discussion the group prioritised four key areas where research
147 design considerations restrict translation of findings into practice: features of the
148 intervention under evaluation; appropriate selection of outcome measures; demonstration
149 of superiority / non-inferiority of the intervention according to the outcome measures
150 selected and strategies to minimise bias within experimental and quasi-experimental study
151 designs. The working group's initial outputs were reviewed by two independent advisory
152 experts, both senior, clinically active antimicrobial stewardship experts in different
153 European countries. Their input prompted widening the group to bring in additional
154 expertise in the field of implementation research, primary care and paediatrics. A second
155 face-to-face meeting the working group used the findings of the systematic review to
156 develop a theoretical framework through which researchers can address these four key
157 research design considerations. The group proposed a series of key questions researchers
158 can use to highlight the major issues they need to address to arrive at an optimal design for
159 their specific research project. Final agreement of recommendations presented here by all
160 eighteen members of the working group was achieved by email.

161

162 A THEORETICAL FRAMEWORK FOR DESIGNING ANTIMICROBIAL STEWARDSHIP 163 EVALUATIONS

164 The impact of intervention design

165 Detailed discussion of how antimicrobial stewardship interventions are designed is beyond
166 the scope of this guidance. However, the design of the scientific evaluation of an
167 intervention depends on how that intervention was designed, and this then may depend on
168 a set of interdependent considerations (Figure 1a). The **intervention rationale** should
169 include its basis in theory and existing evidence. (Table 1 is a glossary of terms used in this
170 guidance). The existing evidence that informed the research question should be clearly
171 explained on an efficacy-effectiveness-implementation spectrum (12), as these
172 considerations will determine how outcomes are selected and prioritized (Figure 1b).
173 Detailed characterization of the **intervention setting** is required to allow assessment of
174 external validity and to minimize selection bias. Stewardship interventions are typically
175 multifaceted and each **intervention feature** must be specified precisely. The same holds for
176 how the intervention's impact will be determined; this will influence definition and selection
177 of outcomes, selection of clusters/sites and feasibility of blinding. The **intervention aims** will
178 be informed by the rationale and setting and will also be key to selecting the **primary** and
179 **secondary outcomes**; whether these will determine effectiveness and safety or how
180 implementation results change antimicrobial use and what data are required to support
181 translation of study findings into practice. These considerations will inform whether the
182 research sets out to determine **superiority** or **non-inferiority** of the intervention measured
183 by its primary outcome(s) against standard practice and the detectable effect sizes/non-

184 inferiority margins, the most appropriate **study design** (e.g. experimental or quasi-
185 experimental) and the **detailed design features**.

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187 **Recommendations regarding selection of outcome measures**

188 When assessing the impact of a stewardship intervention, researchers should aim to
189 consider all intended and potential unintended effects (13-15). Outcome measures can be
190 helpfully grouped into three domains as clinical (typically to assess safety of an
191 antimicrobial-sparing intervention in terms of patient outcome), microbiological
192 (resistance), and care-related (processes and structures of care, sometimes referred to as
193 quality or performance outcomes) (16) (table 2). Whether the study is primarily assessing
194 effectiveness, implementation or a combination of both, will determine how outcomes are
195 selected and prioritised, but, in general, appropriate outcome measures should be
196 prospectively defined from each of the three domains. It is essential to recognise that whilst
197 individually randomised efficacy trials aim to avoid selection bias, the inevitably restricted
198 populations that enter such trials can potentially lead to generalisability bias, making
199 extrapolation to wider populations challenging. While stewardship studies typically assess
200 interventions made at the cluster level, assessment of clinical, microbiological and care
201 related outcomes is often possible at an individual patient level and should be included
202 where possible to address this.

203 ***Clinical outcomes*** are missing from many published stewardship studies. In fact, most of
204 these studies were not sufficiently powered to exclude clinically meaningful harm. Concern
205 that this prevents adoption of antimicrobial reduction strategies into practice has led some
206 to call for routine use of co-primary clinical outcomes in stewardship evaluations (17). The
207 working group felt that clinical outcome measures should always be pre-specified and
208 reported. Exceptions could be implementation studies of interventions for which concerns
209 over safety will not be a barrier to adoption of their findings.

210 **Microbiological outcomes** address the impact of the intervention on antimicrobial
211 resistance and/or rates of *Clostridium difficile* infection. A central rationale for antimicrobial
212 stewardship interventions is that reducing antimicrobial exposure should reduce harm to a
213 patient's microbiome and selection for antibiotic resistance. However, the evidence base
214 remains sparse, and mostly of low quality, with lack of reliable pre-intervention data a
215 particular limitation (9, 18, 19). Incorporating assessment of colonisation/infection by
216 resistant organisms within a stewardship study can be challenging as event rates are often
217 low and the relationship between antimicrobial exposure and resistance may be temporally
218 distant and complicated by interactions with exposure to resistant pathogens and infection
219 control measures. The working group agreed that while reductions in antimicrobial
220 resistance should not be the primary outcome of stewardship studies, measurement of
221 prevalence or incidence of *C. difficile* infection and of antimicrobial resistance should be
222 included in the design where possible, and it should be clear whether measured resistance
223 is in relation to the infecting pathogen and type of infection or among colonising strains.

224 **Care provision outcome measures** (sometimes called quality or performance measures)
225 include process indicators, prescribing behaviours, and antimicrobial use data. These are
226 usually relatively straightforward to obtain and are important to gather and report since
227 clinical outcomes can only be interpreted meaningfully if it is clear that patient management
228 has truly changed. Process indicators may address prescribing quality (e.g. guideline
229 adherence or documentation practice) and reveal mediators of observed results. They are
230 particularly important in implementation research to assess how the intervention under
231 evaluation was actually delivered across the study (fidelity). This allows distinction between
232 strategies that do and do not change the behaviours they aim to change and identification

233 of those elements of an intervention that are impactful and of barriers for implementation
234 (11). Gathering appropriate qualitative data (e.g. from service managers, care providers and
235 patients as appropriate) will allow an intervention's impact on cultural aspects of antibiotic
236 use to be evaluated. Process outcomes are needed to assess organisational impact, of both
237 implementation and long-term sustainability. Sustainability assessment is particularly
238 important when an intervention has significant organisational-level impact through
239 diversion of activity or cost (20). For detailed consideration of these issues researchers
240 should consult current guidance on development and evaluation of complex interventions
241 (21).

242 **Timing of outcome measurements**

243 Within each domain of outcome measure, consideration must be given to appropriate
244 timing depending on the nature of the intervention and population (e.g. long and short term
245 mortality, clinical complications during hospitalisation or after discharge). Timing of
246 measurement of microbiological outcomes should be considered to assess impact on
247 resistance including *C. difficile* and timing of process outcome measurements should be
248 considered to assess long-term sustainability.

249

250

251 **Establishing superiority or non-inferiority**

252 Where a stewardship study sets out to establish the effectiveness of an intervention,
253 incorporation of appropriate controls is essential if the results are to inform practice,
254 irrespective of whether an experimental or non-experimental design is used (see below).
255 Researchers need to decide whether their primary objective is to determine superiority or
256 non-inferiority of the intervention vs control.

257 ***Interventions aiming to improve treatment outcome.*** In some situations, a relevant clinical
258 benefit can be hypothesised for an intervention (e.g. an intervention that focuses on
259 increasing earlier targeted treatment based on test results or preventing under-treatment)
260 and a study assessing the effectiveness of the intervention would seek superiority of the
261 intervention vs. control for an appropriate primary clinical outcome.

262 ***Intervention aims to reduce antimicrobial exposure.*** In most situations, stewardship
263 interventions aim to preserve clinical outcome while reducing unnecessary antimicrobial
264 exposure (e.g. less inappropriate initiation of antibiotics, choice of narrower spectrum or
265 shorter duration) and improving quality of prescribing. As a result there is often some
266 degree of real or perceived risk of patient-level harm, which may be specific to the
267 intervention, patient population, setting and disease. Researchers designing effectiveness
268 evaluations should consider what potential for patient harm would prevent adoption of the
269 intervention ***even if it were effective in reducing antimicrobial exposure.*** Researchers
270 should select appropriate secondary clinical endpoint(s) to address this concern. Ideally in
271 this situation the research should seek both superiority for an appropriate process measure
272 *and* non-inferiority (i.e. not qualitatively worse than control) for a co-primary clinical
273 outcome. The key measure to assess non-inferiority is the non-inferiority margin, being the

274 smallest outcome difference for which the intervention would be considered no worse than
275 control. The size of the non-inferiority margin strongly influences the sample size required
276 to demonstrate non-inferiority with sufficient power. What margin is chosen depends on
277 the outcome selected. The margin needs to be small enough to exclude relevant harm,
278 which would prevent intervention implementation into practice. Researchers should justify
279 the non-inferiority margin chosen with regard to severity and frequency of the outcome in
280 the control group (which may, for example be affected by case-mix (22)).

281 Naturally, trials designed for demonstrating non-inferiority of clinical outcomes usually
282 require large sample sizes. In such trials an interim analysis of a process outcome could be
283 used to determine futility; if the intervention does not lead to the pursued process change
284 continuing that intervention may not be logical, as non-inferiority will be the inevitable
285 outcome.

286 Recognising that achieving adequate power to exclude clinically relevant non-inferiority will
287 not always be feasible, the group felt that researchers should at least specify and report
288 point estimates and confidence intervals for a single prespecified lead clinical outcome.
289 Bayesian analyses may be helpful to directly estimate the probability that intervention is
290 more than 2.5%, 5%, 7.5% etc inferior to control (23). Researchers should also prespecify
291 the clinical outcomes they will use to assess the safety of the intervention, and all available
292 clinical outcome data should be reported, in order to allow future meta-analysis.
293 Unavailability of data should be explained. Unplanned exploratory analyses of clinical
294 outcomes should be reported as such.

295 In studies addressing how interventions with established efficacy should be implemented,
296 the quantitative outcome measures will be predominantly process measures and
297 comparisons will seek to determine superiority of the intervention over comparator.

298 **Sample size calculations**

299 Studies evaluating effectiveness of an antimicrobial intervention need to be powered to
300 demonstrate clinically relevant non-inferiority. In a superiority trial, detecting a large effect
301 with high probability is almost always possible at a feasible sample size. Whereas
302 demonstrating superiority only requires the confidence interval for the effect estimate to
303 exclude zero, regardless of its width, determining non-inferiority requires the entire
304 confidence interval to lie below the non-inferiority margin (24). As a result, much larger
305 participant numbers are usually required to demonstrate non-inferiority within clinically
306 relevant margins which may be very small and difficult to define for outcomes such as
307 mortality (25). This difference lies in that superiority trials tend to be powered on an
308 expected effect, which is often larger than what would be deemed a clinically relevant
309 effect, whereas non-inferiority trials need to be powered on a clinically relevant effect.

310 One proposed solution to this issue is the Desirability of Outcome Ranking (DOOR)/
311 Response Adjusted for Days of Antibiotic Risk (RADAR) approach which uses investigator
312 ranked composite outcomes. This approach is based on the assumption that the same
313 outcome with less antimicrobial exposure is desirable (26). Yet, problems with clinical
314 interpretation and sensitivity to the clinical outcomes chosen have been reported (27, 28). It
315 remains to be determined to what extent the RADAR approach can robustly establish the
316 effectiveness of novel stewardship interventions.

317 Interrupted time series studies require enough sequential measures before and after the
318 intervention; the study's power will depend on the number of data points, their distribution,
319 variability, the expected strength of the intervention effect and confounding factors such as
320 seasonality (29), and therefore there are no straightforward sample size formulae.
321 Researchers should consider the minimal requirements set out in the Cochrane Effective
322 Practice and Organisation of Care (EPOC) resources (30).

323 **Study design**

324 Stewardship interventions typically target prescribers/professionals rather than individual
325 patients. As a consequence, evaluations involving individual patient randomisation are
326 usually not possible because of contamination. Instead, intervention allocation must be
327 clustered (e.g. hospital, ward, primary care practice, or physician). An important advantage
328 of allocation at the cluster level is that it is more representative of real-life clinical practice.
329 It is therefore more suited to studying both antimicrobial use interventions and
330 antimicrobial improvement strategies rather than efficacy. Whereas in individual patient
331 trials, randomisation can be expected to control for confounding bias and maximise internal
332 validity, with cluster randomised controlled trials (cRCT), researchers need to give careful
333 consideration to how clusters are defined and characterised. Clusters should be defined at
334 the lowest level (e.g. clinical team, ward, practice, hospital) where contamination is unlikely
335 as this will maximise the number of available clusters and hence study power. However,
336 with the small number of clusters typically available in stewardship evaluations,
337 randomisation cannot be relied on to avoid imbalance between intervention and control
338 clusters. Therefore baseline imbalances which may influence the intervention's impact (e.g.
339 antimicrobial use, antimicrobial resistance rates, infection control standards, antimicrobial
340 stewardship structures and processes, case-mix of patients) should be specified *a priori* and

341 data on these should be gathered for inclusion in multivariate analyses. Baseline imbalance
342 in factors which a strong association with outcome or that could potentially modify the
343 effect of the intervention can be addressed through stratified randomisation (e.g. putting
344 clusters into similar pairs and allocating one of each pair randomly to intervention vs
345 control), or use of a cross-over design (see below). Cluster characterisation is also essential
346 to understand any observed heterogeneity of the intervention's effect between clusters. It
347 optimises external validity by allowing others to judge the representativeness for their
348 clinical practice and to understand the logistical challenges of implementation.

349 ***Experimental study designs (Table 3)***

350 Three main forms of cluster-randomised design may be appropriate depending on the
351 intervention. As above, ***parallel cRCTs***, in which each cluster is randomised to either the
352 intervention or control, minimise risk of contamination and maximise independence of the
353 intervention from cluster-level characteristics. In some situations, perceptions of the
354 intervention may influence whether clusters are willing to be randomised to control or
355 intervention arms and hamper participation or introduce bias. ***Stepped-wedge cRCTs***
356 ***(swcRCTs)*** overcome this issue since all clusters receive the intervention during the trial, and
357 allow estimation of the intervention effect within each cluster. swcRCTs can be logistically
358 challenging to deliver since some clusters may have to wait to introduce the intervention
359 and exposure should be avoided. Furthermore, the analysis of swcRCT is more complex (31).
360 Randomisation of time of implementation is crucial to ensure independence of the timing of
361 introduction from cluster-level factors. ***Cross-over cRCTs*** offer the potential to estimate
362 intervention effects in both directions – i.e. introducing and withdrawing, but may not be
363 practicable (e.g. it may not be feasible to withdraw an educational intervention).
364 Alternatively, the washout phase of a cross-over study may be considered an assessment of

365 sustainability for some forms of intervention. Assessment of carried antimicrobial resistance
366 in crossover designs may need to consider the potential for resistance selection to persist.

367 A particular challenge with evaluation of interventions made at a cluster rather than
368 patient-level is intracluster correlation (32). This must be incorporated into the sample size
369 calculation otherwise a trial may be underpowered. Intracluster correlation is the extent to
370 which patients are more similar to each other within a cluster than they would be if selected
371 at random. The intracluster correlation coefficient (ICC) of an outcome is a measure of the
372 relatedness of clustered data by comparing the variance within clusters (e.g. hospitals) with
373 the variance between clusters. A high ICC means that observations within clusters are much
374 more similar to each other than to observations in other clusters, while an ICC of zero
375 means that observations within one cluster are equally similar to each other than to
376 observations in other clusters. In general, if the ICC is large, research designs with cross-over
377 are more efficient, while if the ICC is low, parallel cluster designs are more efficient (32).

378 ***Quasi-experimental study designs (Table 4)***

379 In situations where randomisation is not feasible or ethically not acceptable (see below),
380 quasi-experimental, before-after-studies have the potential to deliver robust evidence of a
381 causal relationship between an intervention and measured outcomes if they incorporate
382 appropriate controls and analyses which account for time trends. Where control is provided
383 through comparison with centre(s) where the intervention is not introduced, the term
384 **Controlled Before-After (CBA)** study is used. Where control is provided by use of pre-
385 intervention observations within centres, and secular time-trends in the outcomes are
386 specifically accounted for, the term **Interrupted Time Series (ITS)** study is used. In practice,
387 ITS reflects a method of analysis, being used for before and after studies and CBA, rather

388 than a specific study type and can also be applied to CBA studies. CBA studies which do not
389 control for time-trends are unlikely to provide reliable evidence, regardless of external
390 control (19). The working group agreed that, design of quasi-experimental evaluations of
391 stewardship interventions must always account for changes in time (33, 34). Such analyses
392 require sufficient pre-intervention time points to incorporate segmented regression
393 analysis, and should consider adjustment for autocorrelation (e.g. using ARIMA models).
394 Such analyses should report immediate effects on outcome and trends before and after the
395 implementation, and assess whether trends are non-linear (29, 35). Furthermore the timing
396 of intervention implementation must be externally set to avoid the problem of regression to
397 the mean which occurs when sites introduce a stewardship intervention in response to
398 deterioration in the chosen outcome measure. Detailed guidance on conduct of Interrupted
399 Time Series analyses are available through EPOC (30) and described in a recent review (36).

400 ***Ethical considerations***

401 Antimicrobial stewardship measures which balance immediate and individual risks against
402 future and societal access to effective antimicrobials raise challenging ethical issues around
403 intergenerational justice, global distributive justice and protection of public health (37). A
404 key ethical issue in stewardship research is that, by gathering evidence for safety through
405 clinical outcome measures, the possibility of individual harm is acknowledged. Individual
406 patient consent may not be feasible in studies of interventions which act on prescribers or
407 structures such as hospitals or clinics. This may set a higher ethical barrier than for
408 individually randomized studies in which informed consent can be obtained. In this situation
409 the research design process should involve patients to ensure that independent non-
410 research views from the relevant patient population about these trade-offs are heard,
411 actively considered, and incorporated into the final design. Additionally, researchers should

412 be able to justify why the interventions under examination are reasonable choices of
413 practice which could also be made outside the study setting. Studies in which the
414 intervention is made at a cluster level will often still use individual patient data. Any
415 requirement for individual patient consent to collect data may lead to loss of
416 representativeness and a biased assessment of the intervention effect. Because consent is
417 acquired with knowledge of the intervention, there is an increased risk of selection bias, e.g.
418 if investigators are more motivated to enroll patients during the intervention period.
419 Depending on the national regulations, in some countries study designs can address this
420 issue through use of de-identified or anonymous data (e.g. through electronic patient
421 records) of parameters collected routinely in clinical practice without the need for individual
422 patient consent.

423

424 **KEY DESIGN DECISIONS**

425 The consensus group considered that researchers planning antimicrobial stewardship
426 evaluations must make a set of key decisions (Table 5) which will ultimately determine
427 optimal study design. We have classified these decisions based on whether they apply to
428 the *intervention itself*, the *evaluation setting*, the *outcomes of interest*, the *research*
429 *objective* and *type of study*. Detailed explanation of the decisions are presented in
430 **supplementary materials.**

431 **DISCUSSION AND CONCLUSIONS**

432 The theoretical framework and design recommendations we present have been developed
433 by a diverse international working group with broad and substantial expertise in
434 antimicrobial stewardship research and practice. They address aspects of study design
435 which are crucial to translation of research into practice and will, we believe, increase the
436 impact of future research in this field. By drawing on wide-expertise and building our
437 comprehensive systematic review we consider our recommendations relevant across
438 diverse settings of care. Our work has some notable limitations. Although we gave careful
439 consideration to the breadth of expertise required on the group and sought external advice,
440 we did not seek lay input. We cannot discount the possibility that this would have changed
441 our emphasis, around patient reported outcome or experience measures for example. Given
442 the technical nature of our guidance we think it unlikely this would have changed our
443 conclusions. An inherent risk of the consensus-group design is 'group think' in which
444 members trying to reach consensus fail to critically evaluate alternative views. To address
445 this we sought critical evaluation by two highly eminent international experts in this field.

446 Although these were also, of necessity, experts in antimicrobial stewardship research, the
447 impact of their input on our thinking, the breadth and seniority of expertise in our group
448 make it unlikely we have failed to consider major alternative viewpoints. Notwithstanding
449 these caveats, we believe that application of this guidance has the potential to greatly
450 improve the quality and impact of antimicrobial stewardship research.

451

452

453 **SUMMARY RECOMMENDATIONS**

454 **Outcomes**

- 455 • Researchers should determine whether their study aims to investigate,
456 effectiveness, or implementation ('what or 'how'). This will determine the priority
457 and nature of outcomes.
- 458 • All antimicrobial stewardship studies should define process, clinical and
459 microbiological outcomes and specify a primary process outcome(s) to measure
460 effectiveness of the intervention.
- 461 • Unless there is pre-existing evidence that a stewardship intervention cannot or will
462 not compromise treatment outcome, an evaluation should attempt to pre-specify a
463 co-primary clinical/microbiological efficacy outcome on which the study is
464 adequately powered, or, at minimum, a single lead clinical outcome.
- 465 • Clinical and microbiological data documenting treatment outcome should be
466 collected and reported as pre-specified secondary outcomes even if the study is not
467 powered on them

- 468 • Measurement of incidence of infections / colonisation due to multi-drug resistant
469 bacteria and infections due to *C. difficile* infection should be included in the design of
470 stewardship interventions whenever possible. Studies assessing resistance should
471 clarify whether this is related to the infecting pathogen or among colonisers.

472

473 **Objectives**

- 474 • If a relevant clinical benefit can be hypothesised for an intervention, then the
475 research objective should seek superiority for an appropriate primary clinical
476 outcome.
- 477 • If not, researchers should seek both superiority for an appropriate process measure
478 and ideally non-inferiority for a co-primary clinical/clinically relevant microbiological
479 outcome.
- 480 • Researchers should justify how the non-inferiority margin has been selected and
481 balanced against research costs and feasibility.
- 482 • Where this is not possible, as a minimum, researchers should specify, and report
483 point estimates and confidence intervals for, at minimum, a single pre-specified lead
484 clinical outcome.
- 485 • In situations where the study size is determined by a co-primary non-inferiority
486 safety outcome, an interim futility analysis of the superiority process outcome
487 should be considered to confirm a relevant change in treatment/management.

488

489 **Study design**

- 490 • Cluster randomised controlled trials (including crossover and stepped-wedge
491 designs) are preferable to quasi-experimental before/after studies.

- 492 • The threshold for defining clusters should be as low as possible to minimise
493 contamination, allowing the maximum number of clusters to be studied.
- 494 • In a parallel cluster RCT, randomisation should not be relied on to control for
495 imbalance between study arms if the number of clusters is <20 per arm and
496 stratified or matched randomisation should be considered
- 497 • Designs using within-cluster comparisons (stepped-wedge cRCT, cross-over cRCT or
498 quasi-experimental approaches) are indicated where there are fewer than 10
499 clusters per arm.
- 500 • Quasi-experimental studies should incorporate appropriate controls and analyses to
501 account for time trends
- 502 • In quasi-experimental studies, timing of the intervention should be externally set or
503 if this is not possible timing should be explained and described.
- 504 • Segmented regression analysis of interrupted time series studies should include 12
505 time points with at least 100 observations per time point before and after the
506 intervention to allow for anticipated secular trends and test or correct for
507 autocorrelation.
- 508 • Single centre studies using a robustly designed and analysed interrupted time series
509 approach including observations before and after the intervention should be
510 considered the lowest quality research design which will impact on clinical practice.

511

512

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516

517

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521

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526

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529

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Table 1 Glossary of terms

Term	Explanation
Intervention rationale	The theory and evidence behind the stewardship intervention which is to be evaluated encompassing external factors (e.g. behavioural theory, evidence from previous research) and the clinical setting.
Clinical setting	The environment in which the intervention is evaluated, both physical (e.g. ICU, emergency room, hospital type, primary care, long-term care) and practical (e.g. prescribing practice, team structures, staffing, behaviour).
Intervention aim(s)	The improvement being sought (e.g. reduction in inappropriate antimicrobial prescribing, reduction in use of specific antimicrobial classes or reduced <i>Clostridium difficile</i> infection)?
Features of the intervention	The different elements which make up a multifaceted intervention (e.g. education, decision support).
Cluster	A unit representing a group of smaller components, at which an intervention is delivered (e.g. a hospital ward representing all the doctors working in it, a group of primary care physicians working in a practice)
Outcomes of interest	The outcomes measured to determine effectiveness, safety and costs of the intervention.
Experimental design studies	Studies which use randomisation to allocate the stewardship intervention and control, either to individual patients/professionals or clusters of patients/professionals.
Quasi-experimental design studies	Studies which don't use randomisation to allocate the stewardship intervention but rather use as controls different time period(s) and/or site (s), either external (controlled before-after studies) or internal (interrupted time series analyses, before-after studies).
Contamination	Unintended exposure of patients in the control phase or cluster to some or all of the intervention.
Efficacy study	A study which assesses whether an antimicrobial use intervention produces the expected result under ideal and controlled conditions.
Effectiveness study	A study which assesses whether an antimicrobial use intervention produces the expected result under 'real-world' pragmatic conditions.
Implementation Study	A study which assesses the impact of an antimicrobial use improvement strategy in daily practice
Mediator analyses	Techniques to investigate mechanisms through which complex interventions achieve an observed effect
Superiority analysis	An analysis which sets out to determine if the intervention or strategy being assessed is better than comparator
Non-inferiority analysis	An analysis which sets out to determine whether the intervention or strategy being assessed not worse (by a prespecified amount, the non-inferiority margin) than

	comparator
Process Indicators	Measures of the care that is actually delivered to the patients (e.g., empirical regimen according to guideline)
Structure indicators	Measures of the organization of the healthcare system (e.g., the availability of a stewardship team)
Ecological assessment (of antimicrobial resistance)	Measurement of burden of antimicrobial resistant organism(s) or gene(s) in the environment or aggregated patient samples

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Table 2: Outcome measures in antimicrobial stewardship evaluations

Clinical outcome measures;	
Examples	Notes
Clinical cure, clinical failure, time to clinical response, recurrence rate. Mortality, length of stay, need for escalation of care (e.g. from ward to high dependency or critical care), (re)admission to hospital, revisits Patient reported outcomes (e.g. quality of life measures).	Typically used to determine the safety of the intervention in terms of patient treatment outcome. May include microbiological evidence of clinical outcome (e.g. microbiological cure or recurrence). Most are directly relevant to the individual patient. Important safety outcomes which are relatively easy to gather at cluster-level, but may only be linked partially to the intervention and may be a long way down the patient pathway.
Adverse drug reactions, drug–drug interactions	Gathering relevant data may require individual consent but could be from a subset of patients or use anonymised electronic records.
Microbiological (resistance) outcome measures	
Examples	Notes
Colonisation by antimicrobial resistant pathogens (e.g. MRSA or multi-drug resistant (MDR) Enterobacteriaceae)	Valuable as short-term surrogate measures of antimicrobial resistance-related harm but relevance to individual patients is indirect through risk of antimicrobial resistant infection in the future or through transmission. Ecological assessments may be more feasible than individual patient-level measurement.
Infection by specific organisms (<i>C. difficile</i> , antimicrobial resistant bacteria)	Outcome directly relevant to the impact of the antimicrobial intervention on the individual patient but uncommon and may require long follow-up beyond that needed for clinical outcomes
Care provision (quality or performance) outcome measures	
Examples	Notes
Drug use (e.g. Defined daily doses (DDD) or Days of Therapy (DOT) per admission or per bed-day Appropriateness of treatment (e.g. proportion of prescriptions in accordance with guidelines) Measures of intervention (e.g. recommendations given, use of clinical decision support) Resource requirements (e.g. staff time, clinical consultations, diagnostic	Measurement of antimicrobial use (e.g. volume, range of agents) used to determine whether the intervention has potential to have an effect on clinical or microbiological outcomes (if no impact on process, then no clinical/microbiological impact by definition) Can be selected to measure appropriateness of antimicrobial selection Important for health-economic analyses and assessment of sustainability Important for mediator analyses.

testing) Costs measures	
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Table 3. Design recommendations for experimental evaluations antimicrobial stewardship Interventions

Feature	Recommendations		
	Parallel cRCTs	Stepped-wedge cRCTs	Crossover cRCTs
Cluster selection	Randomised implementation at the lowest level (e.g. prescriber, ward, hospital, primary care practice) at which contamination can be minimised Define eligibility criteria and document representativeness of included clusters with respect to system from which they are drawn (e.g. size, case mix)		
Cluster allocation and randomisation, timing of intervention	Ensure allocation concealment until the intervention is implemented (as complete blinding to allocation after randomisation is often not feasible).	Conceal timing and order of intervention / cross-over as much as possible Timing of intervention should be determined externally and at random, where possible	
Cluster balance	Pursue good/excellent balance between clusters (e.g. matching, stratified randomisation based on factors likely to be associated with the outcome under study). No lower limit above which randomisation will ensure balance but particularly problematic if there are fewer than 20 clusters per randomised group. Collect data to document balance between clusters.	Good/excellent balance between clusters achieved through design.	
Blinding	Consider the objectivity of the selected outcomes and the extent to which patients and assessors of outcomes can be blinded to the cluster allocation		
Outcomes	Specify a primary or co-primary process outcome Specify a co-primary clinical outcome or at minimum one lead clinical outcome, and specify and report secondary clinical outcomes even if not powered on these Specify and analyse outcomes in each domain – clinical, microbiological, process (quantity or quality of antimicrobial use)		

	<p>Within implementation research, process outcomes should be selected with regard to complex intervention methodology [21] e.g. measures of fidelity, mediators and modifiers of the intended effect and measures of organisational impact</p> <p>Consider all important harms / unintended effects including ‘squeezing the balloon’ effects in which achieving the intended reduction in antimicrobial overuse results in an unintended increase in harmful overuse elsewhere [14, 15, 38].</p> <p>Define timing of different cluster-level and individual-level outcomes</p>	
Power calculation	Provide sample size calculations to demonstrate study power – for the primary / co-primary outcome(s), and taking intra-cluster correlation into account	
Analysis	Adjust for secular trends (particularly for stepped-wedge cRCTs)	
Selection of patients for outcome evaluation	<p>Ensure robust consistent inclusion of patients in control and intervention clusters / phases.</p> <p>Report denominators from whom included patients were selected wherever possible.</p>	
Follow-up of patients	Timing of patient follow-up to assess patient-level outcomes should consider relevant timescales for both effectiveness and harms	
Follow-up of clusters	Consider duration of follow up both for immediate effect of the intervention and sustainability	Only possible with short-term interventions with rapid loss of effect post withdrawal
Reporting	Report according to CONSORT criteria for cluster RCTs, stepped-wedge cRCTs, and other CONSORT guidelines as appropriate (e.g. pragmatic trials, non-inferiority trials). Consider using the TiDier checklist to clearly describe any behavioural intervention [39].	

Table 4. Design recommendations for quasi-experimental evaluations antimicrobial stewardship Interventions

Feature	Recommendations
Control	<p>Even in situations where randomisation is not possible (e.g. too few available clusters) allocation to intervention or control group should be made externally if at all possible, i.e. not depending on known factors or clinician preference</p> <p>Consider trying to match controls to minimise risk of bias arising from intrinsic differences between control and intervention groups</p>
Timing	<p>Timing of intervention should be externally set OR if this is not possible timing must be explained and described</p>
Data	<p>Data from automated electronic data recording (e.g. antimicrobial use data, routine electronic patient data) can be used retrospectively for pre-intervention data providing that collection/entry is consistent over calendar time, otherwise all data should be collected prospectively</p> <p>Measure, report and analyse any concurrent changes in case-mix, changes in methodology of outcome assessment, and care practices</p>
Analysis	<p>Include at least 12 monthly time points before and after the intervention to allow for anticipated secular trends [36, 40]</p> <p>Use segmented regression or ARIMA models to account for secular trends.</p> <p>Include at least 100 observations per time point [40].</p> <p>Check and, if necessary, correct for autocorrelation.</p>
Outcomes	<p>See table 3</p>
Follow-up of patients	<p>Timing of patient follow-up to assess patient-level outcomes should consider relevant timescales for both effectiveness and harms</p>
Follow-up of clusters	<p>Consider duration of follow up both for immediate effect of the intervention and sustainability</p>
Reporting	<p>Report according to relevant recommendations; STROBE-AMS [41] or STROBE [42] and the TiDier checklist [39], SQUIRE to describe in detail quality improvement component of study [43], TREND statement for nonrandomized evaluations of behavioural and public health interventions [44].</p>

Table 5. Key Design Decisions. A detailed explanation of the rationale and how these address different aspects of design is set out in the supplementary materials

Question	Design aspect addressed
Where does knowledge gap the study aims to address lie on a spectrum between 'what' and 'how' questions?	selection and prioritisation of outcomes
What are the risks of contamination?	how clusters will be defined within the study.
Is it possible to remove the intervention after it has been implemented?	what study design will be most appropriate.
Is the intervention impact threatened by sustainability?	selection and timing of study outcomes
What forms of bias threaten the validity of the study?	cluster selection; feasibility of blinding; data collection
What features of the evaluation setting will impact on external validity?	cluster selection; feasibility of blinding; data collection
Is it possible to blindly assess the outcome?	feasibility of blinding

Figure 1A. Interacting considerations relating to the intervention to be evaluated and their impact on study design



Figure 1B. An evaluation pipeline for antimicrobial stewardship intervention. Adapted from [12].

