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Comparative Effectiveness Research 2

Generating comparative evidence on new drugs and devices after approval

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1 **Summary**

2 Certain limitations of evidence available on drugs and devices at the time of market
3 approval often persist in the post-marketing period. Too often, post-marketing research
4 landscape is fragmented. When regulatory agencies require pharmaceutical and device
5 manufacturers to conduct studies in the post-marketing period, these studies may remain
6 incomplete many years after approval. Even when completed, many post-marketing studies lack
7 meaningful active comparators, have observational designs, and may not collect patient-relevant
8 outcomes. It is crucial for regulators, in collaboration with the industry and patients, to ensure
9 that the important questions that are unanswered at the time of drug and device approval are
10 resolved in a timely fashion during the post-marketing phase. We propose a set of seven key
11 guiding principles that we believe will provide the necessary incentives for pharmaceutical and
12 device manufacturers to generate comparative data in the post-marketing period. First, regulators
13 and pharmaceutical companies (for drugs), notified bodies and manufacturers (for devices)
14 should develop customised evidence generation plans, ensuring that future post-approval studies
15 address any limitations of the data available at the time of market entry that would influence the
16 benefit-risk profiles of drugs and devices. Second, post-marketing studies should be designed
17 hierarchically: priority should be given to efforts aimed at evaluating a product's net clinical
18 benefit in randomised trials compared with current known effective therapy, whenever possible,
19 to address common decisional dilemmas. Third, post-marketing studies should incorporate
20 active comparators as appropriate. Fourth, use of non-randomised studies for the evaluation of
21 clinical benefit in the post-marketing period should be limited to instances when the magnitude
22 of effect is deemed to be very large or when it is possible to reasonably infer the comparative
23 benefits or risks in settings where doing a randomised trial is not feasible. Fifth, efficiency of
24 randomised trials should be improved by streamlining patient recruitment and data collection
25 through innovative design elements. Sixth, governments should directly support and facilitate the
26 production of comparative post-marketing data by investing in the development of collaborative
27 research networks and data systems that reduce the complexity, cost, and waste of rigorous post-
28 marketing research efforts. Seventh, financial incentives and penalties should be developed or
29 more actively reinforced.

30
31

32 The turn of 21st century marked a period when a number of high-profile safety concerns
33 for commonly-used treatments brought significant attention to the role of regulatory agencies in
34 protecting public health.^{1,2} For example, rofecoxib, a nonsteroidal anti-inflammatory drug that
35 was approved by the FDA in 1999, was withdrawn from the market in 2004 after a series of
36 studies found that it increased the risk of major cardiovascular events.^{3,4} The rise and fall of
37 rofecoxib brought into sharp focus the limitations of the post-marketing research landscape that
38 had until then relied on ad-hoc efforts to generate data on newly-approved drugs and devices.⁵

39 Acknowledging the need to monitor and evaluate drugs not only prior to their approval
40 but throughout their life span, regulators in Europe and the US have since adopted a “lifecycle”
41 approach. There has been significant progress on the post-marketing safety evaluation of drugs
42 both in Europe and the US, as represented by the Sentinel initiative in the US,⁶ and the
43 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) in
44 the European Union⁷ (see **Online Appendix**). Although similar efforts are currently underway
45 for devices, such as the National Evaluation System for health Technology in the US, NEST,
46 these are still in their infancy.⁸ Post-marketing safety surveillance of medical devices remains
47 decentralised in Europe.⁹

48 Together with safety, post-market evaluation of clinical benefit for drugs and devices is
49 important for two reasons (**Figure 1**). First, an increasing proportion of approvals have recently
50 benefited from regulatory programs aimed at expediting the development and review of new
51 drugs.¹⁰ Regulators created expedited programs to address unmet patient need in certain serious
52 and debilitating conditions. Approvals in such programs typically rely on earlier-stage data than
53 what is traditionally required for market entry.¹¹ Second, regulatory agencies have recently
54 articulated their vision for a future where the line separating pre-approval and post-approval
55 periods is blurred. Instead of making binary decisions as to whether a new treatment should be
56 approved or rejected on the basis of available data, regulators are adopting so-called “adaptive”
57 approaches to iterative data collection and evaluation throughout the life-span of therapies.¹²
58 Historically, evidence standards for medical device approvals have been substantially lower than
59 those for drugs (even more so in Europe); post-approval evaluation is therefore essential.¹³

60 There are significant challenges associated with relying on post-marketing research to
61 address the limitations of data generated on clinical benefit prior to approval.¹⁴ The relatively
62 little investment on post-approval data needs has led to a fragmented research environment.¹⁵
63 Consequently, the key limitations of the data available on the clinical benefit of drugs and
64 devices at the time of market approval have largely persisted in the post-marketing period.

65 In this second article of the *Series*, we focus on the potential for generation of
66 comparative effectiveness evidence in the post-marketing period and its coordination with pre-
67 approval research efforts. Our focus is on drugs and devices (implantable and high-risk devices),
68 however the issues and principles covered in this article apply more broadly to other
69 interventions, such as surgery or even health policy interventions. We first review some of the
70 current key challenges of post-marketing research and its three important methodological
71 features: study designs, endpoints and types of comparators. We then propose strategies to
72 improve the future availability of comparative data on new drugs and devices after market entry.

73

74 ***Current post-marketing research landscape***

75 Once drugs are approved by regulatory agencies, research activity on their clinical
76 benefits is primarily influenced by regulatory and market forces.¹⁶ Regulatory agencies in both
77 Europe and the US frequently recommend the completion of post-marketing studies to address
78 the uncertainties that remain at the time of drug approval. For drugs approved through some
79 expedited programs (accelerated approval in the US and conditional marketing authorisation in
80 Europe), regulators may also have post-marketing study *requirements*. In fact, continued market
81 availability of certain expedited drugs may be conditional on the timely completion of such
82 mandatory post-marketing studies. Although the FDA can require post-approval studies for
83 high-risk devices, the lack of a centralised regulatory agency for medical devices in Europe
84 means that post-approval evaluation of benefit remains ad-hoc under the discretion of notified
85 bodies.¹⁷ In terms of market forces, following marketing authorisation, pharmaceutical
86 manufacturers have a limited period of time (usually 10-12 years) during which they have market
87 protections on their approved products. During this period, companies naturally have incentives
88 to invest in research to broaden the approved indications of their products.

89

90 *Regulatory agency-driven research in the post-marketing period*

91 According to a recent evaluation of FDA approvals from 2009 to 2012, the vast majority
92 of post-marketing commitments, which are not required by any statute or regulation, were for
93 non-clinical studies.¹⁸ Often, post-marketing studies required by regulatory agencies are
94 insufficiently described and do not contain enough information to characterise important study
95 design features such as comparators, randomisation, and endpoints.¹⁹ This is partly because post-
96 marketing studies are rarely underway (or even designed) at the time of market entry. In a recent
97 systematic review, median times permitted by FDA for pharmaceutical companies to submit
98 protocols for their required post-marketing studies ranged from 3 to 15 months after approval.²⁰

99 Post-marketing commitments and requirements may remain incomplete many years after
100 approval.¹⁴ Pharmaceutical companies seldom meet regulatory deadlines in the post-marketing
101 period: only half the studies started in 2009 and 2010 had been completed by the end of 2015,
102 and some companies failed to submit required annual status reports, with the FDA rarely
103 imposing penalties for lack of due diligence.²¹ For drugs that received FDA's accelerated
104 approval from 2009 to 2013, almost half of incomplete studies were either terminated or delayed
105 by more than one year.²² Of the 93 new cancer indications that received FDA's accelerated
106 approval between 1992 and 2017, 51 (55%) fulfilled their post-marketing requirements and
107 verified clinical benefit, 37 (40%) indications did not complete confirmatory trials or verified
108 benefit, and 5 indications (5%) were withdrawn from the market, as they did not show clinical
109 benefit when confirmatory post-approval trials were completed.²³ Perhaps even more critical
110 than the timeliness of these trials is that they generate sufficient reliable evidence on proven
111 effectiveness of therapies to guide future practice long term. For instance, the recently reported
112 results of ANNOUNCE, a large RCT of olaratumab in patients with advanced or metastatic
113 soft-tissue sarcoma, did not confirm an apparent survival benefit of olaratumab in combination
114 with doxorubicin as compared to doxorubicin alone, a standard-of-care treatment and its FDA
115 approval has now been withdrawn.²⁴

116 In Europe, EMA implemented 69 obligations for 26 conditionally-authorized medicines
117 between 2006 and 2016. Over a third of these obligations were subsequently changed and more
118 than half had delays in data submission.²⁵ Two of the 26 drugs were ultimately withdrawn from
119 the market for commercial reasons, ten were switched to regular approval, and 14 were still
120 under conditional approval, oftentimes several years after market entry.^{26,27}

121 Even when required confirmatory studies are completed, they resemble the design
122 features of pre-marketing studies. Studies about drugs targeting rare conditions have similar
123 designs as those investigating drugs treating non-rare conditions in the post-marketing period.²⁸
124 Among novel therapeutic agents that received accelerated approval between 2000 and 2013,
125 clinical benefit was often confirmed in post-marketing trials which had similar design elements to
126 preapproval trials, including reliance on non-randomised designs, and surrogate endpoints.²²
127 Cancer drugs approved by the FDA based on the surrogate endpoint of response rate were often
128 tested in post-marketing studies that captured other similar surrogate endpoints.²⁹

129 Among high-risk therapeutic devices approved via FDA's most stringent pathway for
130 medical devices, implementation of post-approval studies has been challenging.³⁰ According to
131 one review, only approximately 13% of initiated post-marketing studies were completed between
132 three and five years after FDA approval.³¹ No corresponding figures are available from Europe;

133 historically, any relevant post-marketing requirements by notified bodies have not been publicly
134 disclosed. The revised Medical Device Regulations, which will come into effect in May 2020 will
135 require public disclosure of such information in the European Union Database for Medical
136 Devices (EUDAMED).³²

137

138 *Industry-initiated research in the post-marketing period*

139 Most new drugs have industry-initiated post-marketing studies; however, the majority of
140 these are conducted in therapeutic areas outside of the approved indication (or including
141 participants that extend beyond the indicated population).²⁸ Such studies could be useful if they
142 produce unbiased evidence on clinically relevant outcomes for the original approved indication
143 and beyond. Instead, companies conduct post-marketing studies to seek approvals in new
144 indications or expand their already-approved indications.^{33,34} In addition, most post-approval
145 studies are small and many are not designed to directly evaluate the clinical benefits of newly-
146 approved drugs.³⁵ In a large systematic evaluation, the quantity and quality of post-approval
147 clinical evidence varied substantially for novel drugs first approved by the FDA on the basis of
148 limited evidence, with few controlled studies published after approval that confirmed clinical
149 benefit using clinical outcomes for the original FDA approved indication.³⁶ Post-approval
150 evaluation of high-risk devices is sparse.³¹

151 Evidence to date suggests that valid data confirming the clinical benefits of drugs and
152 devices on the basis of patient-centred and clinically-relevant outcomes may not routinely
153 emerge in the post-marketing period.³⁷ According to a recent study, only one-fifth of required
154 post-marketing studies of cancer drug indications approved via the FDA's accelerated approval
155 pathway over the past quarter century demonstrated improvements in overall survival in
156 randomised controlled trials, though patients may occasionally derive quality of life benefits in
157 some limited cases without a survival gain.³⁸

158

159 *Coordination of evidence generation between before and after approval*

160 The nature of the current post-marketing research contributes to the well-known
161 problem of research waste.³⁹ To produce medical knowledge that is clinically informative and
162 satisfies the goals of different stakeholders, increased coordination over the life-course of a
163 product is required. It is, therefore, crucial for regulators, in collaboration with patient groups,
164 health technology assessment organisations, payers, pharmaceutical and device manufacturers,
165 and public funders, to ensure that the important questions that are unanswered at the time of
166 approval are resolved in a timely fashion during the post-marketing phase.

167 While some regulatory flexibility in approval standards is important in therapeutic areas
168 with significant unmet need, such cases warrant a careful examination of the gap between the
169 existing (what is available) and the optimal (what is needed) evidence that is required for decision
170 making in clinical practice and health policy. If planned carefully, post-marketing studies on
171 drugs and devices can generate timely evidence across the lifecycle of a medical product to
172 reduce the substantial residual uncertainties at the time of regulatory approval.

173

174 *What is the “optimal” quantity and quality of evidence to inform decision-making in the post-marketing period?*

175 Although it may be difficult to develop universal evidence standards for all therapeutic
176 areas, there are a number of important principles that determine the internal validity and
177 generalisability of research findings.⁴⁰ These principles are summarised by the PICOTS
178 (populations, interventions, comparators, outcomes, time periods, and study designs)
179 framework.⁴¹ Clinical studies supporting the regulatory approval of new drugs and high-risk
180 devices often include highly-selective and narrowly-defined patient populations (P); adopt a strict
181 definition of the intervention implemented in protocol-driven settings (I); examine the clinical
182 benefit of the new product against a placebo or no treatment (C); evaluate surrogate measures of
183 effect rather than clinical outcomes (O); have short follow-up durations (T); and lack important
184 study design elements that are required to establish internal validity, i.e., attribute observed
185 effects to the treatment rather than other factors (S).

186 An important dimension of comparative effectiveness research in the post-marketing
187 period should be to extend the evidence base to patients for whom the current evidence is
188 considered not applicable over a longer period of time and across a broader definition of the
189 intervention. For example, the mean age of patients included in most trials of antiplatelet drugs
190 in secondary prevention of stroke was about 60 years compared to over 75 years in a population-
191 based study.⁴² Although the risk of bleeding complications at age <65 years in the population-
192 based cohort was reassuringly similar to that in the previous trials, both the risk and severity of
193 bleeding complications in patients aged over 75 years was several-fold greater and outcomes
194 were substantially worse.⁴²

195 While it is desirable that post-marketing research efforts address the limitations of the
196 evidence base across the full spectrum of the PICOTS framework, priority should be given to
197 research efforts that are aimed at confirming clinical benefits (new and long-term outcomes) of a
198 new product before setting out to examine its generalisability (expanded patients groups)
199 (**Figure 2**). Our primary focus in this article is on the three key methodological features of post-
200 marketing studies – choice of comparators (C), study outcomes (O), and study designs (S). If

201 data limitations persist on these three features after approval, it remains difficult to establish
202 whether a new drug or device works, and whether it works any better or worse than existing
203 alternatives.

204

205 *Choice of comparators*

206 Less than a third of studies in the published clinical literature adopt active comparators⁴³
207 and only 22% of studies registered in clinicaltrials.gov have active comparators with the
208 remainder employing either placebo or no control.⁴⁴ Clinical trials with active comparators are
209 more likely to be sponsored by non-commercial funders, including governments.^{43,44} Some of the
210 largest, and most influential, comparative effectiveness trials in the post-marketing period have
211 been publicly funded. For example, one of the landmark comparative effectiveness trials in
212 psychiatry, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which
213 was funded by the US National Institutes Health, compared in a head-to-head fashion the
214 relative effectiveness of second-generation antipsychotic drugs with perphenazine, an older
215 agent, for the treatment of patients with chronic schizophrenia and found that they were not
216 significantly different in overall effectiveness.⁴⁵ Another publicly-funded comparative
217 effectiveness trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack
218 Trial (ALLHAT), showed that inexpensive thiazide-type diuretics were more effective than some
219 of the newer treatment classes.⁴⁶

220 Comparative effectiveness studies need not always be undertaken as head-to-head
221 comparisons, especially when the addition of therapies to standard care is being considered. A
222 factorial (or partial factorial design) may be preferred in some instances. For instance, the Second
223 International Study of Infarct Survival (ISIS-2) trial showed that the addition of aspirin or
224 streptokinase provided added benefit over not giving either treatment.⁴⁷

225 Most comparative effectiveness research sponsored by manufacturers focus on their own
226 products. Previous examinations of the geometry of treatment networks in different therapeutic
227 areas have revealed key insights about the preferences of industry sponsors regarding
228 comparators when designing their research studies.⁴⁸ Industry-sponsored studies are not
229 necessarily of lower methodological rigour;^{49,50} however, many such studies are designed in a way
230 to produce conclusions in favour of the sponsored intervention by selecting comparators with an
231 inferior benefit or harm profile.⁵¹ The vast literature on antidepressants for depression illustrates
232 this phenomenon.⁵² Therefore, the choice of comparators is one of the primary mechanisms
233 through which trial sponsors shape the cumulative evidence available to guide treatment
234 decisions in the post-marketing period.⁵³ Such practices have long-lasting implications on the

235 relevance of the evidence base for decision-making and highlight the need for regulatory input
236 on the design of post-marketing studies and the conduct of more such studies that are entirely
237 independent of industry sponsors.

238 For some truly innovative treatments, active comparator may not exist. In other cases,
239 identification of active comparators may be difficult. What is essential is that the new therapy is
240 compared with the current best standard of care (which may be in addition to or as an alternative
241 to such standard of care). Since most therapies that benefit from expedited regulatory programs
242 are for conditions with an unmet need and sometimes without a recognised established therapy,
243 the choice of comparator in the post-marketing period may include the best supportive care
244 (such as for patients with advanced cancer having failed all lines of effective therapy). Physician's
245 choice as comparator may also be considered in areas when choosing the appropriate
246 comparator proves difficult.⁵⁴

247

248 ***Choice of study outcomes***

249 Study outcomes can be broadly divided into two categories: *clinical outcomes* and *surrogate*
250 *measures*. Clinical outcomes (such as mortality, morbidity, or health-related quality of life)
251 represent direct clinical benefits that are meaningful to patients and clinicians. Surrogate
252 measures (such as laboratory tests, radiographic images, or other biomarkers that correlate with
253 clinical outcomes), on the other hand, are substitutes for clinical outcomes and typically do not
254 represent direct clinical benefit. An observed correlation between intermediate measures and
255 clinical outcomes – however strong – is not adequate to establish surrogacy; changes in a
256 surrogate measure should also reliably predict changes in the clinical outcome, both at the
257 individual and aggregate levels.⁵⁵ Usually, it is easier to demonstrate the surrogacy of measure at
258 the aggregate level. For instance, low-density lipoprotein (LDL) cholesterol is associated with
259 coronary heart disease, and, on average, lowering LDL-cholesterol reduces the risk of coronary
260 heart disease.⁵⁶ However, specific individuals who suffer coronary events may not always be
261 those with the worst LDL-cholesterol response.

262 Non-validated surrogate measures may fail to predict treatment effects on clinical
263 outcomes. For instance, despite the (inverse) association between high-density lipoprotein
264 (HDL) cholesterol and coronary heart disease, RCTs of investigational therapeutic agents have
265 failed to demonstrate a reduction in coronary heart disease risk by increasing HDL cholesterol
266 levels.^{57,58} Anti-diabetic agents that effectively lower baseline HbA1c levels do not lower the risk
267 of all-cause mortality or deaths due to cardiovascular causes.⁵⁹ In the Cardiac Arrhythmia

268 Suppression Trial, use of encainide and flecainide was associated with excess mortality compared
269 with placebo, despite their effect on a surrogate measure, suppression of ventricular ectopy.⁶⁰

270 Regulatory agencies in both Europe and the US have a long history of approving new
271 treatments on the basis of their effects on surrogate measures alone. Between 2005 and 2012,
272 approximately half of pivotal clinical studies that supported the FDA approval of new drugs
273 used surrogate measures as primary endpoints.⁶¹ Most high-risk device approvals in the US are
274 supported by surrogate measures alone. Surrogate measures have feasibility advantages over
275 clinical outcomes in drug and device development. Surrogate measures typically require smaller
276 sample sizes and shorter study durations to achieve a statistically significant improvement,
277 thereby substantially reducing the cost and complexity of studies, thus possibly allowing faster
278 patient access to new treatments. According to a recent evaluation, using progression-free
279 survival and response rate in cancer trials was associated with an average 11-month and 19-
280 month, respectively, shorter clinical development period compared with using overall survival.⁶²

281 Although certain surrogate measures are well-validated, many of the surrogate measures
282 used for approval decisions are not comprehensively validated, highlighting the need to confirm
283 clinical benefit in the post-marketing period. Surrogate measures are particularly common in
284 cancer trials. More than four fifths of pivotal studies that supported the approval of cancer drugs
285 in the US relied on surrogate measures alone.⁶¹ According to systematic reviews, the relationship
286 between surrogate measures (such as tumour response or progression-free survival) and clinical
287 outcomes (such as overall survival or quality-of-life) is often poor.⁶³⁻⁶⁶

288 Surrogate measures used for approval decisions have important implications for clinical
289 practice and health policy. In some cases, improvements observed on surrogate measures may be
290 false positives. According to a large meta-epidemiological review, clinical studies using surrogate
291 measures produced substantially exaggerated results compared with those using clinical
292 outcomes (with relative odds ratios ranging between 1.28 and 1.48).⁶⁷ In addition, clinical studies
293 using surrogate measures were twice as likely to find “positive” results compared with studies
294 that captured clinical outcomes.⁶⁷

295 For example, bevacizumab was approved for the treatment of metastatic breast cancer
296 on the basis of its effect on progression-free survival. In a subsequent trial, however, there was
297 no evidence that bevacizumab improved overall survival among women with this condition.⁶⁸ In
298 some cases, drugs approved on the basis of surrogate measures alone may turn out to be
299 harmful. In the recent BELLINI trial, patients with relapsed, refractory multiple myeloma who
300 received venetoclax had worse overall survival than those who received the control treatment

301 even though venetoclax appeared superior in terms of its effect on surrogate measures of
302 progression-free survival and response rate.⁶⁹

303

304 *Choice of study designs*

305 The best way to establish the clinical effectiveness of a new treatments to perform a
306 RCT.⁷⁰ In non-randomised studies, treatment assignment is influenced by the patient, the
307 provider, or even the setting, resulting in differences in distribution of prognostic factors in
308 patient groups receiving different treatments. Such confounding by indication (or treatment
309 selection bias) is a material threat to the internal validity of non-randomised studies and explains
310 why clinicians, researchers, and policymakers are often reluctant to use observational studies to
311 reach conclusions about the comparative effectiveness of treatments.⁷¹

312 Despite the intractable problems of confounding, there is growing enthusiasm for
313 expanding the use of non-randomised studies in the regulatory setting, driven in part by the
314 increased availability of routinely collected data, such as electronic health records, and methods
315 to process and analyse these data.^{72,73} The US 21st Century Cures Act, passed in 2016, allows the
316 use of non-randomised studies when approving new indications for already-approved drugs.⁷⁴
317 While non-randomised studies are helpful in monitoring the safety profiles of treatments, they
318 have well-known validity limitations when determining the clinical effect of treatments (of either
319 benefit or harm) with small-to-moderate effect sizes.⁷⁵

320 Many methods exist that try to control for confounding in non-randomised studies.
321 Some of them (such as propensity score adjustment and instrumental variables) have become
322 more popular over time,⁴³ but it cannot be secured that such approaches control confounding
323 effectively.⁷⁶ When instrumental variables were used, non-randomised studies failed to control
324 for one or more potentially major confounders, which could lead to over-estimation, under-
325 estimation or complete reversal of the effect estimate.⁷⁷ While researchers and regulatory
326 agencies continue to develop approaches to address confounding and bias in non-randomised
327 studies, it will still be important to understand fitness of use and ensure validity for a given
328 context.

329

330 *Generating comparative effectiveness in the post-marketing period*

331 We recommend seven strategies which may promote and facilitate the generation of
332 post-marketing comparative effectiveness research aimed at addressing the limitations of the
333 evidence available on new drugs and devices at the time of approval (**Table 1**).

334

335 1. Ensure post-marketing studies address clinically important evidence gaps

336 In 2012, the Institute of Medicine in the US recommended implementing a Benefit and
337 Risk Assessment and Management Plan to capture in a single “living” document the FDA’s
338 evaluation of the known benefits and risks during the entire life cycle of the product.^{78,79} This
339 recommendation has not been adopted, highlighting the challenges associated with establishing
340 and continuously monitoring the fast-evolving evidence base on approved products. Without
341 such a document or living library, however, it is not possible for regulators, health technology
342 assessment organisations, payers, clinicians, and patients to stay abreast of the evolving research
343 on new products. When a new product enters the market, it remains difficult for stakeholders in
344 the health system to characterise and quantify the remaining uncertainties on its benefits,
345 especially in relation to the optimal amount of evidence needed to inform decisions. Regulatory
346 agencies are uniquely positioned to summarise what *is* and *is not* known about the comparative
347 benefits and harms of new products when they enter the market. One exception is the notified
348 bodies in Europe, as they do not conduct the evaluation of evidence submitted by device
349 manufacturers.

350 With input from patient groups, health technology assessment organisations in Europe
351 and the federal and state-level payers in the US, FDA and EMA should develop a customised
352 plan to guide subsequent post-marketing research efforts and ensure that future studies
353 correspond directly to the limitations of the data available at the time of market entry. In
354 Europe, the recently published guidance on the Summary of Safety and Clinical Performance for
355 high-risk and implantable medical devices will require manufacturers to summarise “if there are
356 any unanswered questions relating to the use of the device.”⁸⁰ Although health technology
357 assessment organisations and payers differ in their evidence requirements, post-marketing
358 research plans could focus on a minimum set of core principles that are shared among different
359 stakeholders,⁸¹ namely the choice of comparators, study outcomes, and study designs.

360

361 2. Design post-marketing studies hierarchically

362 In recent years, an increasing proportion of new products have entered the market on
363 the basis of non-randomised studies that lack active comparators and include only surrogate
364 measures.⁸² When data on drugs and devices deviate from the optimal quantity and quality of
365 evidence, manufacturers should be required by regulators to confirm their clinical benefit in a
366 timely manner.¹⁴ The industry’s drug and device development plans should include a detailed,
367 feasible, and timely research plan for generating this evidence. Even though post-marketing
368 studies aimed at extending the approved indication could generate useful evidence on the

369 effectiveness and safety of products, such studies should not commence before the studies set
370 out to demonstrate clinical benefit within the original indication are well underway.³⁶

371 Drugs and devices approved on the basis of earlier-stage data (i.e., without active
372 comparators, using only surrogate measures as study outcomes, in non-randomised studies)
373 should be required by regulators in the post-marketing period to demonstrate their benefits in
374 randomised trials with active and clinically-meaningful comparators that measure patient-centred
375 clinical outcomes that belong to the set of core outcomes for the disease of interest. Although
376 the regulatory agencies currently lack the statutory authority to require such studies outside of
377 certain programs (e.g., accelerated approval pathway in the US), legislative change should be
378 sought to enable such requirements.

379 Requiring additional studies in the post-marketing period need not adversely affect
380 investment in drug and device development. In 2008, the FDA issued guidance on the need for
381 outcome trials to assess the cardiovascular safety of new diabetes drugs. Since the FDA's
382 guidance, the research and development landscape for diabetes has significantly improved, with
383 several products demonstrating a positive effect on cardiovascular outcomes.⁸³ Evidence to date
384 suggests that FDA's regulatory action has not negatively affected drug development.⁸⁴

385

386 3. Consider a range of active comparators: alternative drugs, devices, and non-drug treatments

387 In therapeutic areas with an established standard of therapy, post-marketing studies
388 should adopt active comparators. Post-marketing studies may need to keep pace, in a more
389 adaptive fashion, with evolution in usual care. It is sometimes challenging to choose the most
390 appropriate comparator. Network meta-analysis could help identify the best active comparator
391 and address uncertainties in the available evidence base.⁸⁵ Industry sponsors have an obligation
392 to test the comparative benefits and harms of their new products against existing alternatives.
393 However, given the importance of this research agenda and the evidence so far suggesting that
394 industry has not always fulfilled this responsibility, independent organisations should play a
395 greater role in designing and running post-marketing trials, ideally leveraging funding from
396 industry (*see recommendation 7*).

397 Public and non-governmental funders such as the Patient-Centred Outcomes Research
398 Institute in the US and the National Institute for Health Research in the UK should prioritise
399 sponsoring research studies comparing different treatments (e.g., medical therapy vs. device;
400 drug vs. exercise intervention), including alternative service packages, care pathways, and digital
401 treatments.⁸⁶ Informative studies may pit one treatment strategy against another (e.g.,
402 psychotherapy vs drug treatment; digital therapeutic options vs. traditional therapeutic options).

403 Yet, such ground-breaking comparative effectiveness studies are too rare, in part due to the
404 difficulty in designing and conducting such studies. Identifying the appropriate types of
405 outcomes, comparisons, and follow-up durations is difficult in trials that compare different
406 treatment categories, and patients and public should be actively and routinely involved in this
407 process.

408 Until relatively recently, only about a tenth of comparative effectiveness studies
409 published in high-impact general medical journals compared pharmacological and non-
410 pharmacological interventions.⁴³ In a recent systematic review of almost 400 randomised trials,
411 there were no direct head-to-head comparisons of antihypertensive drugs and structured exercise
412 interventions in terms of their blood pressure-lowering effects.⁸⁷ Similarly, in a previous meta-
413 epidemiological review, there was a paucity of randomised trials that directly compared the
414 mortality benefits of drug and non-drug interventions in major chronic conditions.⁸⁸ In the
415 absence of such evidence, clinical practice guidelines typically focus on different categories of
416 interventions in isolation and important public health questions are still unanswered.

417

418 4. Use non-randomised study designs more selectively

419 Non-randomised study designs have a clear role for the post-market evaluation of safety,
420 especially for rare or uncommon adverse effects.⁸⁹ However, their role in the evaluation of more
421 common effects of either harm or clinical benefit is contested. For example, the evidence of
422 harm associated with rofecoxib was only fully realised after an analysis of ongoing RCTs. When
423 evaluating clinical benefit, we recommend limiting the use of non-randomised studies in the
424 post-marketing period to settings when the evidence of benefit is very large.⁹⁰ According to
425 previous theoretical and simulation studies, very large effects are those when a treatment appears
426 at least 5 or 10 times more effective than its comparator.⁹⁰⁻⁹² Validity of non-randomised studies
427 can be strengthened by mandatory centralised pre-registration of analytical protocols and public
428 availability of collected datasets.⁷²

429 Non-randomised studies could also be used to evaluate whether drugs and devices with
430 an optimal evidence package can be extended to populations outside of those included in RCTs.
431 In the non-randomised EXPRESS study,⁹³ urgent treatment of transient ischaemic attack and
432 minor stroke with aspirin, blood pressure-lowering medication, and statin resulted in a reduction
433 in 90-day recurrent stroke risk of 80% (adjusted hazard ratio: 0.20, 95% CI: 0.08-0.49). Although
434 the magnitude of this effect was substantially larger than that obtained from previous RCTs,⁹⁴
435 these findings triggered a re-analysis and time-course evaluation of individual participant data
436 from RCTs of aspirin versus placebo. This re-analysis confirmed the dramatic treatment effect

437 observed in the non-randomised study, which was due to an acute benefit of aspirin on the 90-
438 day risk of recurrent stroke that had not been detected in the previous analyses of RCTs.⁹⁵
439 Notably, EXPRESS was nested in a population-based incidence study of all transient ischaemic
440 attack and stroke with near-complete ascertainment of all patients and outcomes before and after
441 the change in treatment practice, thereby reducing the selection biases inherent in non-
442 randomised studies, as well as maximising external validity – the study included all patients in the
443 underlying population with the condition.

444

445 5. Improve the efficiency of randomised trials

446 While RCTs in the post-marketing period can adopt simpler “pragmatic” designs (as they
447 do not need to comply with strict regulatory agency requirements), they may also require
448 complex design features to capture diverse clinical outcomes that may develop over long time
449 horizons. Therefore, designing studies that are useful in the post-marketing period cannot
450 happen unless there are drastic improvements in the efficiency of RCTs. Costs for clinical trials
451 are very high, especially in the US. The median cost of pivotal regulatory trials was estimated at
452 \$19 million for drugs that received FDA approval between 2015 and 2016.⁹⁶ However, there is
453 significant variation in reported estimates, with cost per recruited patient ranging from \$41 to
454 \$6,990 in different studies.⁹⁷

455 RCTs could benefit from innovative methodological designs (i.e. adaptive design trials,
456 basket trials, registry trials, umbrella protocols), which have their own strengths and weaknesses
457 (**Panel 1**). A key driver of clinical trial expenses is the complexity of patient enrolment, trial
458 procedures and data analysis.⁹⁸ To overcome these problems, a new framework is needed which
459 reduces the amount of transactions needed to get the data from a patient into a database for
460 analysis.

461 For example, the registry-based RCT design leverages data sampling from high-quality
462 registries to facilitate high participant inclusion rates at relatively low costs and, therefore, may
463 offer a robust mechanism by which relevant clinical questions are answered in the post-
464 marketing period. In such trials, online registration identifies patients eligible for inclusion,
465 random allocation occurs in the registry, and study set-up is part of clinical care, including the
466 informed consent process.⁹⁹ Ensuring seamless integration of such trials into routine clinical
467 practice may require buy-in from care providers and substantial investment from governments.
468 Another necessary precondition for registry-based trials is the existence of a high-quality registry
469 covering the population to be studied, as the quality of the study data is bound by the quality of

470 the data in the registry.¹⁰⁰ Registries (as those in the Nordic countries and in the UK) offer a
471 potential source of relevant data.^{101,102}

472

473 6. Invest in data infrastructure for comparative effectiveness research

474 Electronic health records, administrative data, and clinical registries currently exist in
475 silos in health care systems. Efforts are underway to build collaborative data infrastructures by
476 linking and leveraging information obtained from separate sources. In compliance with existing
477 regulations to protect the confidentiality of personal data (such as the European General Data
478 Protection Regulation), we recommend accelerating these efforts to facilitate comparative
479 effectiveness research in the post-marketing period,¹⁰³ particularly for facilitating pragmatic
480 RCTs. There are already examples of integrated partnerships involving clinical researchers in
481 academia and industry, patients and institutions, also for medical devices.^{104,105} In 2015, the
482 Patient-Centered Outcomes Research Institute developed a network including patient-powered
483 research networks and clinical data research networks and launched the randomised
484 ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term
485 Effectiveness) trial, which is currently underway, comparing two different aspirin doses in high-
486 risk patients with a history of heart disease.¹⁰⁶ ADAPTABLE reflects a pragmatic design by
487 embedding the RCT within usual care, recruiting a diverse patient population with minimal
488 eligibility criteria, promoting the continuation of usual care without standardised treatment
489 protocols, and relying on electronic data collection with reduced need for costly primary data
490 collection.¹⁰⁷

491 Another US-based initiative, the National Evaluation System for Health Technology
492 (NEST) focuses on medical devices and coordinates the participation of institutions in a data
493 network to develop data quality and methods standards.¹⁰⁸ The first NEST studies involve
494 multiple health systems answering key clinical and safety questions on a range of medical devices
495 from cardiac and orthopaedic implants to catheters used for soft-tissue ablation, intervertebral
496 body fusion devices, and craniomaxillofacial distractors.¹⁰⁴

497 However, progress has been slow, mainly for concerns about the quality and
498 interoperability of underlying data in such systems, as they are not collected for research
499 purposes, and ethical issues regarding data availability and data sharing in non-randomised
500 settings. The future post-marketing research agenda could greatly benefit from the direct
501 engagement of patients by consenting to sharing their electronic data from multiple sources
502 through mobile health apps and electronic platforms, with researchers, regulators and other
503 stakeholders. Concerns about data sharing may pose challenges to such patient-powered research

504 efforts in the post-marketing period.

505

506 7. Create a new set of incentives and reinforce accountability

507 Pharmaceutical and device manufacturers should be held accountable for demonstrating
508 and confirming the clinical benefit of their products in approved indications. Several guiding
509 principles should be considered to reinforce such accountability. First, the level of payment for
510 drugs and devices should correspond to their added benefit according to robust comparative
511 effectiveness studies. Second, longer marketing protections should be considered for products
512 that convincingly demonstrate their superiority to established standards of care.¹⁰⁹ Third, public
513 reporting of best research practices in the post-marketing period may incentivise companies to
514 invest in comparative studies.¹¹⁰ Fourth, regulatory approval may be more formally linked to
515 payer policies such as coverage with evidence development whereby the treatment is only
516 available within the context of an ongoing post-marketing clinical trial.¹¹¹ However, such
517 strategies should be used very selectively and designed carefully so that they do not place undue
518 administrative burden on public payers.

519 In terms of penalty mechanisms, regulatory agencies should more actively consider
520 license suspensions, indication restrictions, monetary fines, or even market withdrawal on a case
521 by case basis. FDA and EMA already have the statutory authority to impose monetary penalties
522 for not completing some required studies in a timely manner in expedited programs for drugs.
523 However, regulators currently lack the administrative capacity and financial resources to exercise
524 these powers.¹¹² Therefore, regulators have yet to penalise pharmaceutical manufacturers for not
525 generating post-marketing data with due diligence. In Europe, the proposal to implement a
526 conditional marketing authorisation pathway for high-risk and implantable devices was rejected,
527 severely restricting attempts at enforcing accountability. This should be the focus of future
528 legislative change. Experience to date suggests that sizeable penalties may be effective to change
529 industry behaviour. Some of the largest corporate fines for criminal offences (imposed by the US
530 Department of Justice and not by regulators) have been for pharmaceutical companies for off-
531 label promotion of their products.¹¹³ Such financial penalties and the media coverage associated
532 with them affected subsequent marketing practices and use.^{114,115}

533

534 ***Conclusions***

535 Comparative evidence on the benefits and harms of new and existing drugs and devices
536 rarely emerges in the post-marketing period. There is an opportunity to coordinate research
537 efforts between before and after approval. Policymakers and regulators can incentivise the

538 generation of comparative data in the post-marketing period by ensuring that post-marketing
539 studies directly correspond to the limitations of pre-approval studies; designing post-marketing
540 studies hierarchically (first to confirm clinical benefit and then to examine generalisability);
541 limiting the use of non-randomised study designs when evaluating clinical benefit; improving the
542 efficiency of randomised trials; investing in data infrastructure; and creating new incentive and
543 penalty mechanisms.
544

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550

551 **Contributors**

552 HN and AC conceived and designed the study. AC wrote the first draft of the manuscript. All
553 other authors contributed to the writing of the final version of the manuscript, and agreed with
554 the results and conclusions of this Article.

555

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562

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570

571 **Panel 1. Innovative (or non-conventional) study designs for randomised trials.** This panel
572 aims to outline key features of selected innovative trial designs. Adaptive trials use information
573 generated during trial conduct to alter subsequent operations in a pre-specified way. In 2018 the
574 FDA provided a draft guidance on “master protocols”, which refer to a master (or core)
575 protocol, upon which multiple questions can be asked about the effectiveness of interventions
576 for a particular disease or condition. Novel trial designs that use master protocols include basket,
577 umbrella and adaptive platform trials. Both elements (master protocol and adaptive design
578 features) add complexity, but with the intent of improving the efficiency of knowledge
579 generation. Registry-based trials include a randomisation module in a large inclusive clinical
580 registry with unselected consecutive enrolment, to combine the advantages of a prospective
581 randomised trial with the strengths of a large-scale all-comers clinical registry.

582

583 ***Adaptive trials***

584 Adaptive trials are designed to maximise flexibility, without compromising the validity and
585 integrity of the trial. Modifications (“adaptations”) to aspects of the ongoing trial can be pre-
586 specified and prospectively planned, including adding or dropping treatment arms, changing
587 dosages, sample size re-estimations and alterations. Adaptive trials aim to identify the patients
588 who are most likely to benefit from a treatment:

- 589 • When single or multiple different disease populations are studied
- 590 • When single or multiple interventions are studied; adaptive trials can utilise multiple
591 therapies
 - 592 ○ The sample size can vary significantly from very large to small depending on the
593 study sub-design, interim sample size reassessments are also utilised
- 594 • *Use:* Both exploratory and confirmatory clinical trials
- 595 • *Advantage:* Reduces the use of resources, decreases the time of trial completion, limits the
596 number of participants allocated to inferior interventions and improves the probability of
597 success of the trial
- 598 • *Disadvantage:* Subject to operational bias, due to the leakage of interim results and the
599 potential to influence investigator behaviour

600

601 ***Basket trials***

602 Basket trials are used to test the effect of a single drug, or a combination of drugs on single
603 mutation (a single target) in multiple diseases (“baskets”):

- 604 • When multiple disease populations are being studied

- Including different histology types or different tumour types, often referred to as 'histology *independent*'
- When a single intervention is studied, which is targeted, matched or is biomarker specific
 - The sample size is relatively large but typically smaller than umbrella trial sample sizes and are generally single-arm trials
- *Use:* Commonly discovery-based trials used in early stages of development
- *Advantage:* An efficient way of identifying if a drug targeting a specific genetic mutation in one site of the body may be effective in treating that same genetic mutation found in tumour located in a different part of the body
- *Disadvantage:* The use of the underlying assumption that molecular profiling is a sufficient replacement of histological tumour typing

616

617 ***Platform trials (or adaptive platform trials)***

618 (Adaptive) platform trials are able to study multiple interventions in a disease or condition in a
619 perpetual manner, with interventions entering and leaving the platform on the basis of a
620 predefined decision algorithm.

- When a single disease population is studied, usually limited to a single disease or single histology/tumour type
 - A broad cohort of participants are enrolled, and later stratified into different subtypes based on clinical or biomarker criteria
- When multiple interventions are studied; they utilise multiple therapies in a perpetual trial design
 - Large sample sizes are often required as platform trials have the capacity to add and drop trial arms as futility or efficacy are demonstrated, often using a decision algorithm
- *Use:* Can range from proof of concept studies through to confirmation of application trials
- *Advantage:* Platform enables characterisation of the safety and efficacy of novel treatment combinations, potentially across diseases, mechanisms and sponsors, that would otherwise not be feasible in one trial
- *Disadvantage:* Potential complexity of the trial implementation and planning, often requiring complex collaborations across sponsors and participating sites

637

638

639 ***Registry-based trials***

640 Registry trials are pragmatic trials that use registries as platforms for health records, data
641 collections, randomisation and follow-up. The advancement of electronic data collection systems
642 has led to the increasing number of developed registries used for research, policy, and
643 administrative purposes. A clinical registry can be used for collection of baseline variables and to
644 identify eligible patients for a study:

- 645 • When single or multiple different disease populations are studied
- 646 • When single or multiple interventions are studied
 - 647 ○ Typically use large sample sizes as large observational cohorts of patients.
- 648 • *Use:* Often later on in drug development, and not suitable for trials that need
649 comprehensive safety reporting or intense pharmacokinetic or pharmacodynamic
650 profiling
- 651 • *Advantage:* Low cost, enhanced generalisability of findings (real-world setting), rapid
652 consecutive enrolment and follow-up
- 653 • *Disadvantage:* Variable data quality, potentially poorly defined variables, limited facility to
654 collect detailed safety reporting

655

656 ***Umbrella trials***

657 Umbrella trials are designed to evaluate the impact of different drugs on different mutations in a
658 single type of cancer:

- 659 • When a single disease population is studied: trials are limited to a single disease or single
660 histology/tumour type
 - 661 ○ Multiple biomarker matched subgroups of patients are used, patients are assigned
662 to biomarker subgroups using a biomarker allocation algorithm
- 663 • When multiple interventions are studied; umbrella trials utilise multiple therapies
 - 664 ○ Large sample sizes are often required, patients with multiple biomarkers can be
665 included in more than one trial arm
- 666 • *Use:* Can range from proof of concept studies to confirmation of application trials
- 667 • *Advantage:* Capacity to draw meaningful conclusions specific to a tumour type
- 668 • *Disadvantage:* Flexibility is limited, due to use of a single tumour type, particularly with
669 rare diseases, where further subclassification may lead to poor accrual.

670

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- 693

694 **Table 1.** Strategies aimed at incentivising pharmaceutical and device manufacturers to generate comparative data on drugs and high-risk and
 695 implantable devices in the post-marketing period, with a summary of the key recommendations and the target stakeholders.
 696

Overall strategies	Key recommendations	Target stakeholders (in alphabetical order)
(1) Ensuring post-marketing studies address evidence gaps	<ul style="list-style-type: none"> • Develop a customised plan to guide subsequent post-marketing research efforts • Ensure that future studies correspond directly to the limitations of the data available at the time of market entry 	<ul style="list-style-type: none"> • Health technology assessment organisations • Public payers • Regulatory agencies (FDA and EMA)
(2) Designing post-marketing studies hierarchically	<ul style="list-style-type: none"> • Products approved on the basis of studies without active comparators should be required to have active-comparators (or controlled trials compared with an known effective control)*. • Products approved on the basis of surrogate measures alone should be required to confirm their clinical benefit on patient-relevant outcomes. • Products approved on the basis of non-randomised study designs should be required to have randomised trials. • Once randomised trials with active-comparators and clinical outcomes are available, post-marketing research efforts should pivot to evaluating the applicability of evidence to broader patient populations over longer time horizons. 	<ul style="list-style-type: none"> • Device manufacturers • Pharmaceutical manufacturers • Regulatory agencies (FDA and EMA) • Government research funding bodies
(3) Considering active comparators beyond drugs and devices	<ul style="list-style-type: none"> • Network meta-analyses should be used to choose appropriate active comparators. • Active comparators should include non-pharmacological interventions. 	<ul style="list-style-type: none"> • Device manufacturers • Government research funding bodies • Non-governmental research funders • Pharmaceutical manufacturers
(4) More selective use of non-randomised study designs	<ul style="list-style-type: none"> • When evaluating clinical benefit, non-randomised studies should be used only when the evidence of benefit is overwhelmingly positive. • When randomised trials are available, non-randomised studies should be used to evaluate applicability to populations outside of those included in trials. 	<ul style="list-style-type: none"> • Device manufacturers • Government research funding bodies • Non-governmental research funders • Pharmaceutical manufacturers • Regulatory agencies (FDA and EMA)

-
- (5)** Improving the efficiency of randomised trials
- Randomised trials should adopt innovative design elements to improve efficiency of patient recruitment and data collection.
 - Device manufacturers
 - Government research funding bodies
 - Non-governmental research funders
 - Pharmaceutical manufacturers
-
- (6)** Investing in data infrastructure for comparative effectiveness research
- Efforts aimed at establishing collaborative research networks and data systems should be accelerated.
 - Governments
-
- (7)** Creating a new set of incentives and reinforcing accountability
- Payment for new drugs and devices should correspond to their added benefit over existing alternatives.
 - Health technology assessment organisations
 - Penalties should be invoked for not generating comparative data in the post-marketing period.
 - Public payers
 - Regulatory agencies (FDA and EMA)

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* Active comparator trials may include head to head comparisons of a new product with a known effective treatment; the addition of the product to current effective treatment versus that same treatment used alone; and placebo-controlled trials of the new product when given in addition to best standard care. The essential requirement is that the new product (alone or in combination) is being compared with a known effective therapy.

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