Online Research @ Cardiff

information services
gwasanaethau gwybodaeth

1   **What the public think about participation in medical research during an influenza pandemic –**

2   **an international cross-sectional survey**

3

4   **Authors**

5   Nina Gobat*, PhD, Nuffield Department of Primary Care Health Sciences, University of Oxford,

6   England, United Kingdom

7   Prof Christopher C. Butler, FMedSci, Nuffield Department of Primary Care Health Sciences, University

8   of Oxford, England, United Kingdom

9   Jill Mollison PhD, Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences,

10   University of Oxford, England, United Kingdom

11   Prof. Nick A. Francis, PhD, Division of Population Medicine, School of Medicine, Cardiff University,

12   Wales, United Kingdom

13   Micaela Gal, DPhil, Division of Population Medicine, School of Medicine, Cardiff University, Wales,

14   United Kingdom

15   Victoria Harris, PhD, Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences,

16   University of Oxford, England, United Kingdom

17   Prof Steve A.R. Webb, PhD, University of Western Australia, Perth, Australia

18   John-Paul Byrne, PhD, University College Dublin, Ireland.

19   Angela Watkins, BA (Hons), Division of Population Medicine, School of Medicine, Cardiff University,

20   Wales, United Kingdom

21   Prasanth Sukumar MPhil, University College Dublin, Ireland

22   Prof Kerenza Hood, PhD, Centre for Trials Research, Cardiff University, Wales, United Kingdom

23   Prof Alistair Nichol, PhD, HRB funded Irish Critical Care-Clinical Trials Network, St Vincent's

24   University Hospital-Clinical Research Centre, University College Dublin, Ireland and the Alfred

25   Hospital and Australian and New Zealand intensive Care- Research centre, Monash University,

26   Melbourne, Australia.

27

28   Corresponding author: Nina Gobat, Nuffield Department of Primary Care Health Sciences, University

29   of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG,

30   nina.gobat@phc.ox.ac.uk, +44 7913416907

31

34

35   **ABSTRACT**

36   **Objectives:** The public and patients are primary contributors and beneficiaries of pandemic-relevant

37   clinical research. However, their views on research participation during a pandemic have not been

38   systematically studied. We aimed to understand public views regarding participation in clinical research

39   during a hypothetical influenza pandemic.

40   **Study design:** International cross-sectional survey

41   **Methods**: We surveyed the views of nationally representative samples of people in Belgium, Poland,

42   Spain, Ireland, United Kingdom, Canada, Australia and New Zealand, using a scenario-based

43   instrument during the 2017 regional influenza season. Descriptive and regression analyses were

44   conducted.

45   **Results:** Of the 6804 respondents, 5572 (81·8%) thought pandemic-relevant research was important

46   and 5089 (74·8 %) thought "special rules" should apply to make this research feasible. Respondents

47   indicated willingness to take part in lower-risk (4715, 69·3%) and higher-risk (3585 52·7%) primary

48   care, and lower-risk (4780, 70·3%) and higher-risk (4113, 60·4 %) Intensive Care Unit (ICU) study

49   scenarios. For primary care studies, most (3972, 58·4%) participants preferred standard enrolment

50   procedures such as prospective written informed consent, but 2327 (34·2%) thought simplified

51   procedures would be acceptable. For ICU studies, 2800, (41·2%) preferred deferred consent and 2623

52   (38·6%) preferred prospective third-party consent. Greater knowledge about pandemics, trust in a

53   health professional, trust in government, therapeutic misconception and experience of ICU as a patient

54   or carer predicted increased willingness to participate in pandemic-relevant research.

55   **Conclusions:** Our study indicates current public support for pandemic-relevant clinical research.

2

56 Tailored information, and initiatives to advance research literacy and maintain trust are required to

57 support pandemic-relevant research participation and engagement.

58

Highlights

- There is strong public support for pandemic-relevant clinical research initiatives.

- Willingness to participate in research and to be enrolled under more permissive approaches depends on the type of research and key participant factors.

- Knowledge about pandemics, trust in professionals and in government, therapeutic misconception and experience of critical illness influence willingness to participate in pandemic-relevant research.

59

60 **INTRODUCTION**

61 The centenary of the 1918 Influenza pandemic presents a stark reminder of global vulnerability to

62 infectious disease health threats[1]. One third of the global population became infected, resulting in 50-

63 100 million deaths. Advances in science, technology, medicine, health systems, and coordination

64 mechanisms have strengthened global preparedness to respond to future pandemics[2]. However, as

65 evidenced during the 2009 H1N1 pandemic, insufficient capability to rapidly generate evidence through

66 clinical research implemented during the pandemic itself results in significant gaps in our preparedness

67 for pandemics. Emerging data from clinical research is vital to inform public health responses, for

68 example, through robust disease severity assessments that account for clinical presentation across the

69 illness severity spectrum[3] and to inform clinical management guidelines[4,5]. During the H1N1 pandemic,

70 clinical management guidelines were necessarily based on expert opinion as scientific evidence was not

71 available. Expert guidance recommended use of oseltamivir, for example, which was widely prescribed

72 to patients with acute respiratory infections at significant cost to healthcare systems. However, the

73 opportunity to evaluate the clinical and cost effectiveness of oseltamivir in prospective trials was

74 missed, as intervention studies could not be delivered in time to enrol patients during the pandemic

75 itself[3] and little evidence was generated about the prudence of stockpiling these antiviral agents.

76 Oseltamivir is now widely regarded as standard of care for the treatment of patients at higher risk of

77 complications from influenza, despite no available prospective trial evidence to support its use in

78 severely ill patients[6], and this now presents an ethical dilemma for its evaluation in a randomised

79 placebo-controlled trial. The newly launched WHO global influenza strategy includes research and

80 innovation for diagnostics, vaccines and treatments as one of four priorities for pandemic preparedness[7].

81

82 There are multiple and persistent political, contractual, administrative, logistic and regulatory

83 challenges that must be navigated for clinical studies to be open for recruitment in time to enrol patients

84 during peak pandemic waves. One approach to unblocking these barriers involves pre-funding active

85 clinical research networks, such as those in the Platform foR European Preparedness Against (Re-

86)emerging Epidemics (PREPARE). PREPARE conducts multi-site, pan-European clinical studies in

87 community, hospital and critical care settings that address important study questions during inter-

88 pandemic periods of seasonal influenza. These research active networks would re-orientate their inter-

89 pandemic research activities in the event of a public health emergency, thereby reducing the time needed

90 to recruit and prepare research sites. PREPARE clinical trials employ novel adaptive platform designs

91 with response adaptive randomisation that shortens the time to identifying a superior performing

92 treatment[8-10] These trials evaluate the comparative effectiveness of routinely available treatments and

93 allow for rapid inclusion of an additional trial arm to evaluate novel therapeutics if these become

94 available.

95

96 The success of these initiatives, however, is dependent on research and clinical staff being willing to

97 enrol patients[11], and patients being willing to participate. Research enrolment processes that are time

98 consuming, unnecessarily detailed and burdensome will deter patient enrolment, even among those

99 patients who would be otherwise willing to participate[12] Existing enrolment models will likely be ill

100 suited to the highly pressured conditions of pandemic-relevant research[13] and less burdensome, risk

101 proportionate consent models may be acceptable. In addition, residual clinical samples e.g. nasal swabs

102 and blood samples, collected and stored after clinical procedures would be an important resource for

103 pandemic relevant ID research and development of new diagnostic tests. Currently these samples are

104   not routinely stored, and consent for using and sharing samples and associated clinical data for research

105   and test development, vary between countries, presenting a challenge to multi site, pan-European

106   research efforts[14,15].

107

108   As the primary contributors and potential beneficiaries of pandemic-relevant research, patients and the

109   public are key, and often underrepresented, stakeholders in research preparedness. While these groups

110   have been consulted for public health pandemic planning[16-19], there have been no systematic efforts to

111   capture their views relevant to participation in clinical research conducted during an influenza

112   pandemic. Further, understanding public views should inform preparations for appropriate,

113   proportionate regulation and oversight of pandemic-relevant research. To advance preparedness to

114   deliver a clinical research response in a pandemic scenario, we aimed to address this gap.

115   **METHODS**

116   We conducted an international cross-sectional survey involving a nationally representative sample of

117   respondents in each of Belgium, Spain, Poland, Ireland, the United Kingdom, Canada, Australia and

118   New Zealand. These countries were selected as involved with or affiliated to the PREPARE consortium.

119   European member states were selected to include a country from each of northern, southern, eastern

120   and western Europe, as defined by the United Nations macro geographical regions[20]. These countries

121   were also included in qualitative work that informed the survey development. Respondents aged 18-

122   65years in each country, except Poland (age range 18-59 years), were invited via a pre-recruited online

123   panel hosted by the Ipsos Group. Ipsos Group is a market research company that regularly conducts

124   online research for academic institutions. This group administered data collection. Ipsos Group

125   generated quotas on age, gender, employment status and region in all countries, setting targets based on

126   the most up-to-date census data to ensure that the sample profile was in-line with the nationally

127   representative proportions in that country. Ipsos Group addressed any small imbalances in the sample

128   by weighting the final data set. All analyses used weighted data.

129

130   *Data collection*

131   Data were collected via an online survey in March 2017 in Northern hemisphere countries and in July

132   –Aug 2017 in Southern hemisphere countries, to coincide with regional influenza seasons. Potential

133   respondents were invited to take part in the survey in batches, in order to control the sample profile.

134   Data collection was planned to continue until the target sample size (850 per country, 6800 total) was

135   reached. The selection of the sample size was pragmatically driven and involved balancing the size of

136   the sample that we would need to identify differences between countries with the cost of administering

137   the survey via Ipsos Group across multiple countries.

138

139   *Data collection instrument*

140   We developed a scenario-based instrument in which respondents were asked to imagine there is an

141   influenza pandemic and they were being invited to participate in clinical research in primary and critical

142   care settings (Box 1; supplementary material). In both scenarios, respondents were asked for their views

143   on taking part in a low and higher risk clinical trial, and to indicate their preferences related to

144   notification and consent for participating in the low-risk study. Low risk scenarios involved comparison

145   of two medications that were routinely used in everyday clinical practice. Higher risk scenarios involved

146   patients receiving either a new medication that had passed safety testing or a placebo. Finally,

147   respondents were asked for their views on the acceptability of any surplus clinical samples (blood or

148   swabs for example), that had been collected as part of clinical care, being subsequently used for

149   pandemic research, without explicit patient consent being solicited for their use. We used illustrations

150   to enhance brief explanations of key concepts.

151   To develop the survey tool, we consulted the public in four European countries[12] to identify content

152   domains for the survey (July-November 2015). We reviewed relevant literature[5,13,21-23] and sought

153   expert opinion to prioritise content domains. We also identified demographic and attitudinal variables[12]

154   that might explain willingness to participate in pandemic-relevant research. These variables included

155   age, being a parent, having had experience of critical illness (as a patient, family member or close friend

156   of a patient) and therapeutic misconception[24] (i.e. research participants holding a belief that research

157   usually or always results in individual benefits as opposed to understanding that the purpose of research

158 is to produce generalizable findings relevant to a population). To refine the wording and response format

159 of the survey questions, we conducted cognitive interviewing using the think aloud technique[25].

160 Changes to the survey were made iteratively, at three time points. The data collection instrument was

161 circulated for comment to colleagues in Belgium, Spain, Poland, Australia and New Zealand to ensure

162 applicability to their healthcare context. The final version of the instrument was translated into Flemish,

163 French, Spanish and Polish and back translated to ensure accuracy. Before the survey was distributed,

164 a small segment of the overall target group of respondents completed the survey and data were reviewed

165 to identify any difficulties. No changes were required following this soft launch.

166 *Analysis*

167 We combined survey responses into three categories (strongly disagree/disagree, neutral and

168 agree/strongly agree) and ran ordinal regression models to examine demographic and attitudinal factors

169 predictive of respondent willingness to participate in primary care and ICU studies and willingness for

170 routinely collected clinical samples to be used for pandemic-relevant research. To identify suitable

171 candidate variables for regression models, we first conducted univariate associations using a chi squared

172 test. Candidates that were significant at $p<0\cdot01$ in univariate analyses were then included. Factors that

173 account for how participants would like to be consented were examined in an exploratory post-hoc

174 analysis using a logistic regression. To explore whether any factors predicted willingness to engage

175 with an alternate approach to consent, we created a binary variable that classified respondents as only

176 willing to consider the standard "Opt in" consent models (box 1) versus willing to consider any of the

177 other options. This variable was used as the outcome in logistic regression models that included only

178 those participants that expressed willingness to take part in each scenario study. In order to assess the

179 impact of missing data at baseline and possible bias arising from data not being missing completely at

180 random (MCAR) the regression models were reanalysed using multiple imputation with chained

181 equations, which is valid under a less restrictive missing at random (MAR) assumption. The results did

182 not differ substantially from the complete case analysis, which suggests there is not substantial bias due

183 to missing data. Data were analysed using STATA version 15.0.

184

Ethics, consent, sponsorship, ethical treatment of human subjects

186 Participants gave voluntary consent for their involvement in the survey. All data were held in

187 accordance with the Data Protection Act.

188

189 **RESULTS**

190 A total of 6804 members of the public completed the survey: 850 in each of Ireland, Spain, Belgium,

191 and New Zealand, and 851 in each of Poland, the United Kingdom, Australia and Canada (table 1).

192 Response rates were not calculated due to the quota sampling technique used.

193

194 *Public attitudes to clinical research*

195 Respondents considered it important that medical research is conducted during an influenza pandemic

196 (5572, 81·9%) and that special rules should apply to make it easier to do pandemic-relevant research

197 (5089, 74·8%). Results were similar across countries, with the exception of respondents from Poland

198 who indicated lower agreement with the importance of medical research in a pandemic (538 of 831,

199 64·7%).

200

201 *Primary Care: willingness to participate in low and higher risk scenarios*

202 A majority of respondents were willing to take part in both the lower risk (4715, 69·3%) and higher

203 risk (3585, 52·7%) primary care study (Figures 1a and 1b). A small proportion of respondents were

204 unwilling to take part in the low risk scenario (792, 11·6%), and 1466 (21·6%) respondents were

205 unwilling to take part in the higher risk scenario. The differences in proportion endorsing each response

206 varied significantly by country (χ^2p<0·001) for both the low and high-risk scenarios (figures 1a and 1b

207 and table 2). Being female (compared with male) was associated with decreased willingness to take part

208 in the high-risk primary care scenario (table 2). For both low and higher risk primary care scenarios,

209 the less knowledge respondents had about pandemics, the lower their reported willingness to take part.

210 Having had ICU experience, trust in a doctor, trust in the government and therapeutic misconception

211 were variables associated with greater willingness to participate in both scenarios (table 2).

212

213   *Primary care: notification and consent preferences for enrolment to low risk CER scenario*

214   Of those respondents willing to take part in the low risk primary care scenario (4715, 69·3%), the

215   majority preferred standard opt-in consent procedures as a first choice (2742, 58·2%), although nearly

216   a third (1371, 29·1%) selected opt-out consent as a first choice (table 3). Automatic inclusion was the

217   least preferred option (461, 9·79%). Of those respondents who indicated willingness to take part in the

218   primary care study, respondents from Spain (compared with the UK) were less likely to accept

219   enrolment under alternate consent models (table 4). A low level of pandemic knowledge was associated

220   with non-acceptance of enrolment under alternative consent models, while having had ICU experience

221   and having greater trust in government were variables associated with acceptance of enrolment under

222   alternate consent models (table 4).

223

224   *ICU: willingness to participate in low and higher risk scenarios*

225   The majority of respondents expressed willingness to take part in both the lower risk (4780, 70·3%)

226   and higher risk (4113, 60·4%) ICU studies (ICU studies (Figures 2a and 2b). A χ^2 test comparing

227   proportion endorsing each response against country was statistically significant (p<0·001) for both the

228   low and high-risk scenarios. Older age groups were associated with being more willing to participate

229   in the higher risk ICU scenario (table 5). A low level of pandemic knowledge was associated with

230   being less willing to participate in both ICU research scenarios. Having had ICU experience, having

231   greater trust in a doctor, greater trust in the government and higher levels of therapeutic misconception

232   were all associated with being more willing to take part in both ICU scenarios (table 5).

233

234   *ICU: notification and consent preferences for enrolment to low risk CER scenario*

235   Of those respondents willing to take part in the low risk ICU scenario (4780, 70·3%), deferred consent

236   given either by a doctor (1345, 28·1%) or a family member (958, 20·0%) were the first choice

237   preferences (table 6). Prospective "opt-in" informed consent procedures was the first choice preference

238   for 35·3% respondents (n=1686). Only 592 (12·4%) respondents indicated that they preferred automatic

239   inclusion (i.e. without consent being provided). Of the respondents who were willing to take part in the

240   ICU study, those that had some experience of ICU, were living with someone rather than alone, and

241   had greater trust in government, were more likely to engage with alternative consent models for the low

242   risk ICU scenario (table 7).

243

244   *Attitudes to use of surplus routinely collected clinical samples for research*

245   5256 (77·2%) of respondents indicated that they would be willing for any surplus of their routinely

246   collected clinical samples to be used for pandemic relevant studies during an outbreak itself, and only

247   slightly fewer 4871 (71·6%) were happy for them to be used after an outbreak without additional

248   consent being sought. 4940 72·6% were willing for their genetic materials to be used for research, and

249   3869 (56·9%) were willing for their samples to be used for non pandemic-relevant studies. A trend for

250   age was observed, with older respondents across each age category being more likely to accept their

251   excess routinely collected clinical samples being used for pandemic-relevant research (table 8). Greater

252   trust in a doctor, greater trust in government and higher levels of therapeutic misconception were

253   associated with willingness for clinical samples to be used for research.

254

255   **DISCUSSION**

256   Members of the public across eight OECD countries support medical research being delivered in

257   response to a pandemic of influenza and a majority of respondents would be willing to take part in

258   medical research in both primary and critical care settings. While the majority of respondents wanted

259   to provide prospective informed consent for enrolment to primary care studies, a substantial minority

260   would consider alternatives. Deferred consent was acceptable to the majority of respondents for

261   enrolment to ICU studies. Pandemic knowledge, trust in health professionals, in government, and

262   experience of critical illness influence indicative willingness to participate. Therapeutic misconception

263   and wanting access to novel therapeutics through trial participation were also predictive of willingness

264   to participate. A majority of respondents were also supportive of their surplus clinical samples being

265   used for research without specific consent.

266

267   A strength of this study is the extensive piloting and refinement used in the development of the survey

268   instrument . We also used images to enhance explanations of core concepts. However, we were unable

269   to fully assess participant interpretation of these ideas and it is possible that some concepts were not

270   uniformly understood. A limitation of the instrument is that it employed hypothetical scenarios and

271   respondent views might change with actual experience. However, respondents' expressed willingness

272   to participate in research has been shown to provide a moderate estimate of actual participation[26]. We

273   do not consider our findings to be a substitute for involvement of the public or for good participatory

274   practice[27] when planning pandemic-relevant studies. Our survey used quota sampling, a non-

275   probabilistic sampling method, and the appropriateness of drawing population wide inferences using

276   this approach has been questioned by some. This was an online survey that required respondents to

277   access the Internet to complete it. Given the high proportion of internet penetration in the countries

278   surveyed in 2017[28], we do not anticipate the digital divide to have impacted on representativeness of

279   the sample. Our findings may be influenced by self-selection bias in that respondents had signed up to

280   an online panel. We are also unable to evaluate the impact of potential nonresponse bias. The survey

281   addressed complex ideas that may not have been uniformly understood. Despite our efforts to address

282   this by using cognitive interviewing in designing the survey, varying interpretation of survey questions

283   represents potential for non-sampling error. Respondents were from countries in the OECD as these

284   were relevant to PREPARE clinical studies and are vulnerable to influenza pandemics. Lower and

285   Middle Income Countries bear the greatest burden of infectious disease outbreaks and findings from

286   our survey do not inform research preparedness in these regions.

287

288   Recent debates regarding comparative effectiveness research have highlighted the inflexibility of

289   standard recruitment processes and argued for more adaptable enrolment protocols in circumstances

290   where informed consent may not be possible, or ethically necessary[29-31]. Others have also identified a

291   substantive minority of respondents supportive of alternate consent procedures for low risk pragmatic

292   trials[32-34]. However, our study is the first to consider this question in the context of a pandemic. Current

293   ethical guidelines[35,36] and new regulations[37] offer some guidance for emergency research and endorse

294   adapted models of enrolment (e.g. deferred consent) where patents lack capacity to consent themselves.

295   Where patients have capacity (for example, enrolment to a primary care trial), even in the event of a

296   public health emergency, current guidelines[35,36] endorse prospective informed consent process

297   regardless of risk through trial participation. Findings from our survey support this approach. In

298   contrast, experience from public involvement in the design of a pre-positioned clinical trial protocol in

299   the UK found that alternatives (verbal consent or opt-out consent) were acceptable[21]. This study was

300   unable to adopt these alternate consent procedures however as they were considered not acceptable

301   under current legislation governing clinical trials of investigative medicinal products (CTIMPs) in

302   Europe.

303

304   This tension between pragmatic and acceptable informed consent processes and guiding legislation

305   represents a notable bottleneck in the viability of clinical research being conducted in a public health

306   emergency. In Europe, the forthcoming Clinical Trials Regulation (No 536/2014)[37] that will govern the

307   conduct of CTIMPs in European Union member states recognises the need for expediting clinical trial

308   applications for approval in a public health emergency, however, no mention is made of acceptable

309   adaptations to consent procedures that are proportionate to study risk or to the context of crisis in the

310   event of a pandemic. This legislation includes a new category of "low intervention" clinical study,

311   recognising that not all clinical trials present the same degree of risk to research participants and

312   simplified informed consent procedures are deemed acceptable for enrolment to "low intervention"

313   cluster trials conducted in a single member state (article 30). However this does not extend to pan-

314   European or individually randomised trials.

315

316   Similar tensions exist in debates about residual clinical samples being used for pandemic-relevant

317   research purposes. Like others who have considered this question[38,39] albeit in a non pandemic context,

318   we identified public willingness to donate excess clinical samples for research. These findings require

319   further consideration in relation to consent requirements for the use of residual clinical samples and

320   associated data[14]. For pandemic-relevant research, sample and data sharing across countries will be

321   important and full de-identification of patient data may not be possible, particularly at the early stages

322   of an outbreak. The General Data Protection Regulation (GDPR), legislation that aims to harmonise

323   and strengthen the rules for protecting individual's privacy rights within the EU may inadvertently

324   create barriers to this process. Clarity regarding interpretation of new EU legislation and the

325 implications for pandemic relevant studies is needed if the significant investment in establishing a

326 clinical research infrastructure to respond to these public health threats can be fully realised.

327

328 Our study found strong support for pandemic-relevant research and a need for wider debate about more

329 permissive approaches to enrol patients into low risk comparative effectiveness research in this context.

330 Experience of critical illness, trust in doctors and in government, and knowledge about pandemics were

331 key explanatory factors. These insights should inform communication and recruitment planning for

332 delivering a pandemic research response, for example, in the PREPARE consortium. Active efforts to

333 engage and involve the public are required in order to build knowledge about pandemics and about the

334 value of research and what research participation in research involves. Key messages, such as

335 uncertainty regarding the superiority of the experimental agent and the purpose of research to produce

336 generalizable results rather than to confer individual benefit, and the distinction between research

337 participation and receipt of clinical care, should be well communicated. For patients, attention to how

338 participation in research is framed, for example, in the wording of participant information sheets can

339 mitigate risk of therapeutic misconception[40]. For the wider public, initiatives that open the way to

340 dialogue and deliberation and that that build research literacy are needed, for example through citizen

341 science and tailored engagement initiatives across communities. Invariably, an infectious disease

342 pandemic will bring with it an epidemic of fear, at which point it will be too late to address these gaps.

343 The research community must be ready to counter the rumours and conspiracy theories that will

344 inevitably circulate with a response that champions the contribution of scientific evidence in protecting

345 health and saving lives.

346

351

373   **References**

374

375   1.   Dicke T. Waiting for the Flu: Cognitive Inertia and the Spanish Influenza Pandemic of 1918–

376   19. *Journal of the History of Medicine and Allied Sciences* 2015; **70**(2): 195-217.

377   2.   Leigh J, Moon S, Garcia E, Fitzgerald G. Is Global Capacity to Manage Outbreaks Improving?

378   – an Analysis. Geneva: Graduate Institute of International and Development Studies, 2018.

379   3.   Simonsen L, Higgs E, Taylor RJ, et al. Using Clinical Research Networks to Assess Severity

380   of an Emerging Influenza Pandemic. *Clinical Infectious Diseases* 2018; **67**(3): 341-9.

381   4.   Commission on a Global Health Risk Framework for the Future G. The neglected dimension

382   of global security: A framework to counter infectious disease crises, 2016.

383   5.   Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a Part of Public Health

384   Emergency Response. *New England Journal of Medicine* 2013; **368**(13): 1251-5.

385   6.   Hurt AC, Kelly H. Debate Regarding Oseltamivir Use for Seasonal and Pandemic Influenza.

386   *Emerging Infectious Disease journal* 2016; **22**(6).

387   7.   WHO. Global influenza strategy 2019-2030. In: WHO, editor. Geneva; 2019.

388   8.   Butler CC, Coenen S, Saville BR, et al. A trial like ALIC(4)E: why design a platform, response-

389   adaptive, open, randomised controlled trial of antivirals for influenza-like illness? *ERJ open research*

390   2018; **4**(2): 00046-2018.

391   9.   Berry SM, Connor JT, Lewis RJ. The platform trial: An efficient strategy for evaluating

392   multiple treatments. *JAMA* 2015; **313**(16): 1619-20.

393   10.   Webb SA, Nichol AD. Bending the Pandemic Curve: Improving Decision-Making With

394   Clinical Research. *Critical Care Medicine* 2018; **46**(3): 442-6.

395   11.   Burns KE, Rizvi L, Tan W, Marshall JC, Pope K. Participation of ICUs in critical care

396   pandemic research: a province wide, cross-sectional survey. *Critical Care Medicine* 2013; **41**(4): 1009-

397   16.

398   12.   Gobat NH, Gal M, Butler CC, et al. Talking to the people that really matter about their

399   participation in pandemic clinical research: A qualitative study in four European countries. *Health*

400   *expectations : an international journal of public participation in health care and health policy* 2018;

401   **21**(1): 387-95.

402   13.   Gobat NH, Gal M, Francis NA, et al. Key stakeholder perceptions about consent to participate

403   in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness.

404   *Trials* 2015; **16**: 591.

405   14.   Rebers S, Vermeulen E, Brandenburg AP, et al. A Randomised Controlled Trial of Consent

406   Procedures for the Use of Residual Tissues for Medical Research: Preferences of and Implications for

407   Patients, Research and Clinical Practice. *PLoS ONE* 2016; **11**(3): e0152509.

408   15.   Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics

409   for infectious diseases. *Clinical infectious diseases : an official publication of the Infectious Diseases*

410   *Society of America* 2013; **57 Suppl 3**: S139-70.

411   16.   Daugherty Biddison EL, Gwon H, Schoch-Spana M, et al. The community speaks:

412   understanding ethical values in allocation of scarce lifesaving resources during disasters. *Annals of the*

413   *American Thoracic Society* 2014; **11**(5): 777-83.

414   17.   Levin D, Cadigan RO, Biddinger PD, Condon S, Koh HK, Joint Massachusetts Department of

415   Public Health-Harvard Altered Standards of Care Working G. Altered standards of care during an

416   influenza pandemic: identifying ethical, legal, and practical principles to guide decision making.

417   *Disaster Medicine & Public Health Preparedness* 2009; **3 Suppl 2**: S132-40.

418   18.   Schoch-Spana M, Franco C, Nuzzo JB, Usenza C, Working Group on Community Engagement

419   in Health Emergency P. Community engagement: leadership tool for catastrophic health events.

420   *Biosecurity & Bioterrorism* 2007; **5**(1): 8-25.

421   19.   Silva DS, Gibson JL, Robertson A, et al. Priority setting of ICU resources in an influenza

422   pandemic: a qualitative study of the Canadian public's perspectives. *BMC Public Health* 2012; **12**: 241.

423   20.   United Nations Statistics Division. Composition of macro geographical (continental) regions,

424   geographical   sub-regions,   and   selected   economic   and   other   groupings.   2016.

425   http://unstats.un.org/unsd/methods/m49/m49regin.htm - europe (accessed First accessed: 3.05.2015;

426   Updated: 29.11.2016.

427   21.   Lim WS, Brittain C, Duley L, et al. Blinded randomised controlled trial of low-dose Adjuvant

428   Steroids in Adults admitted to hospital with Pandemic influenza (ASAP): a trial 'in hibernation', ready

429   for rapid activation. *Health Technology Assessment (Winchester, England)* 2015; **19**(16): 1-78, vii-viii.

430   22.   Venkatesan S, Myles PR, McCann G, et al. Development of processes allowing near real-time

431   refinement and validation of triage tools during the early stage of an outbreak in readiness for surge:

432   the FLU-CATs Study. *Health Technology Assessment (Winchester, England)* 2015; **19**(89): 1-132.

433   23.   GHRF Commission. The neglected dimension of global security: A framework to counter

434   infectious disease crises, 2016.

435   24.   Appelbaum PS, Anatchkova M, Albert K, Dunn LB, Lidz CW. Therapeutic misconception in

436   research subjects: development and validation of a measure. *Clinical trials (London, England)* 2012;

437   **9**(6): 748-61.

438   25.   Jobe JB, Mingay DJ. Cognitive research improves questionnaires. *American Journal of Public*

439   *Health* 1989; **79**(8): 1053-5.

440   26.   Halpern SD, Metzger DS, Berlin JA, Ubel PA. Who will enroll? Predicting participation in a

441   phase II AIDS vaccine trial. *Journal of acquired immune deficiency syndromes (1999)* 2001; **27**(3):

442   281-8.

443   27.   Hankins C. Good participatory practice guidelines for trials of emerging (and re-emerging)

444   pathogens that are likely to cause severe outbreaks in the near future and for which few or no medical

445   countermeasures exist (GPP-EP). WHO: WHO, 2016.

446   28.   Internet World Stats. 2019. https://www.internetworldstats.com/stats4.htm (accessed 13 May

447   2017 2017).

448   29.   Faden RRPDMPH, Beauchamp TLPD, Kass NESD. Informed Consent, Comparative

449   Effectiveness, and Learning Health Care. *New England Journal of Medicine* 2014; **370**(8): 766-8.

450   30.   McKinney RE, Jr., Beskow LM, Ford DE, et al. Use of altered informed consent in pragmatic

451   clinical research. *Clinical trials (London, England)* 2015.

452   31.   Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for

453   randomized, controlled trials? *N Engl J Med* 1999; **340**: 804-7.

454   32.   Nayak RK, Wendler D, Miller FG, Kim SY. Pragmatic Randomized Trials Without Standard

455   Informed Consent?: A National Survey. *Annals of internal medicine* 2015; **163**(5): 356-64.

456   33.   Dal-Ré R, Carcas AJ, Carné X, Wendler D. Public preferences on written informed consent for

457   low-risk pragmatic clinical trials in Spain. *British journal of clinical pharmacology* 2017; **83**(9): 1921-

458   31.

459   34.   Dal-Ré R, Carcas AJ, Carné X, Wendler D. Patients' beliefs regarding informed consent for

460   low-risk pragmatic trials. *BMC Medical Research Methodology* 2017; **17**(145).

461   35.   Council for International Organisations of Medical Sciences. International Ethical Guidelines

462   for Health-related Research Involving Humans. Geneva: CIOMS publications; 2016.

463   36.   World Health Organisation. Guidance for managing ethical issues in infectious disease

464   outbreaks. Geneva; 2016.

465   37.   European Parliament and Council. Regulation (EU) No 536/2014 of the European Parliament

466   and of the Council In: Union E, editor. Official Journal of the European Union: European Union; 2014.

467   38.   Lewis C, Clotworthy M, Hilton S, et al. Public views on the donation and use of human

468   biological samples in biomedical research: a mixed methods study. *BMJ Open* 2013; **3**(8): e003056.

469   39.   Lewis C, Clotworthy M, Hilton S, et al. Consent for the use of human biological samples for

470   biomedical research: a mixed methods study exploring the UK public's preferences. *BMJ Open* 2013;

471   **3**(8): e003022.

472   40.   Christopher PP, Appelbaum PS, Truong D, Albert K, Maranda L, Lidz CW. Reducing

473   therapeutic misconception: a randomised intervention trial in hypothetical clincial trials. *PLoS ONE*

474   2017; **12**(9): e0184224.

475

476

477   Figure 1a: Willingness to take part in low risk primary care scenario
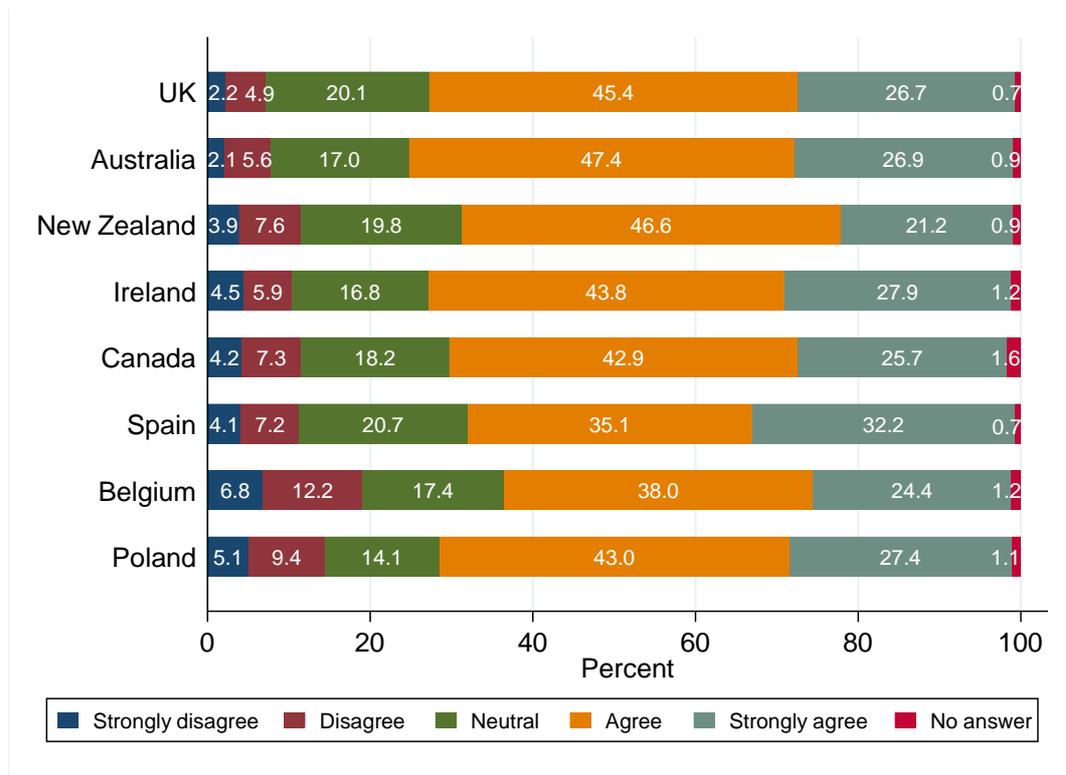
478

479   **Figure 1b: Willingness to take part in higher risk primary care scenario**
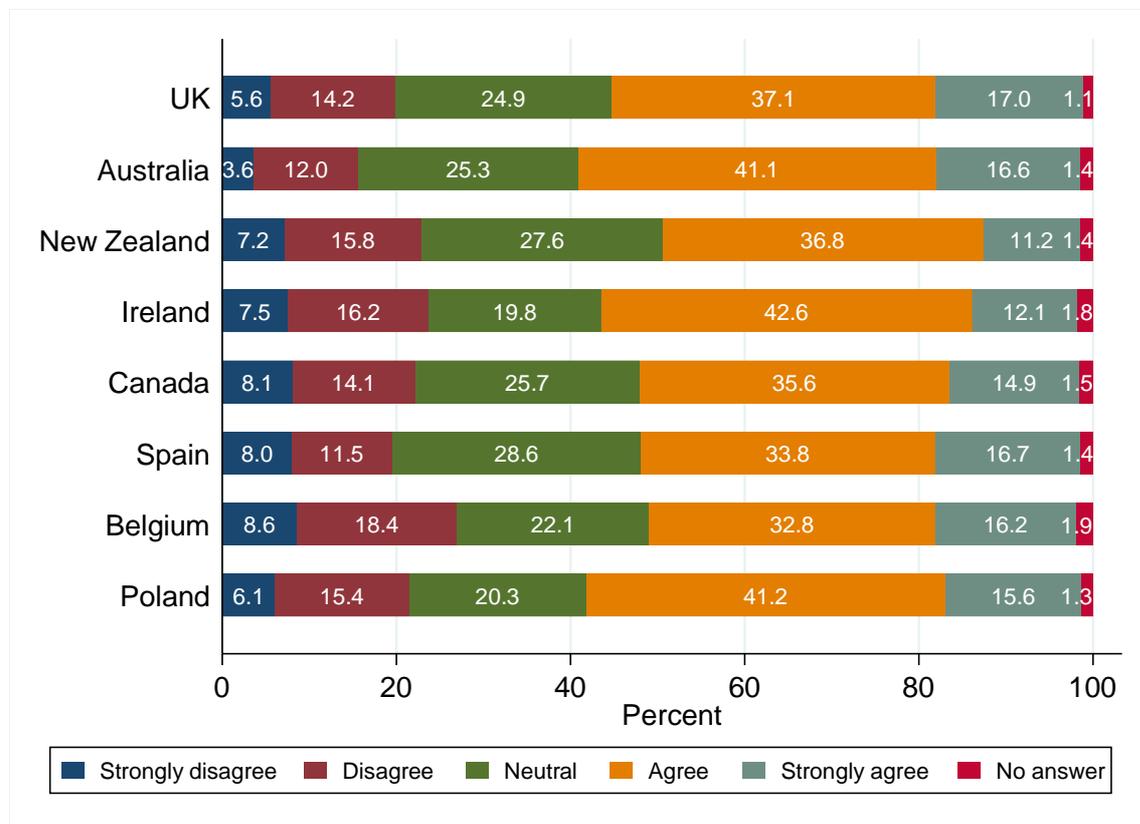
480

481   **Figure 2a Willingness to take part in low risk ICU scenario**
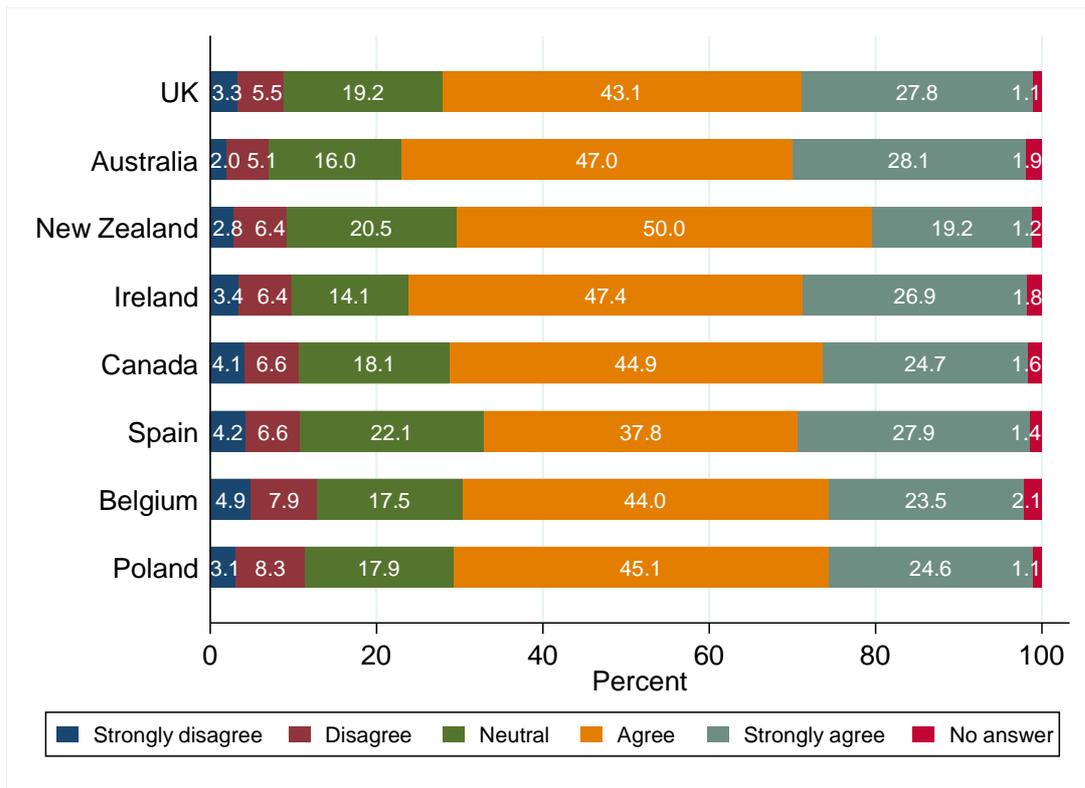
482

483   **Figure 2b Willingness to take part in higher risk ICU scenario**
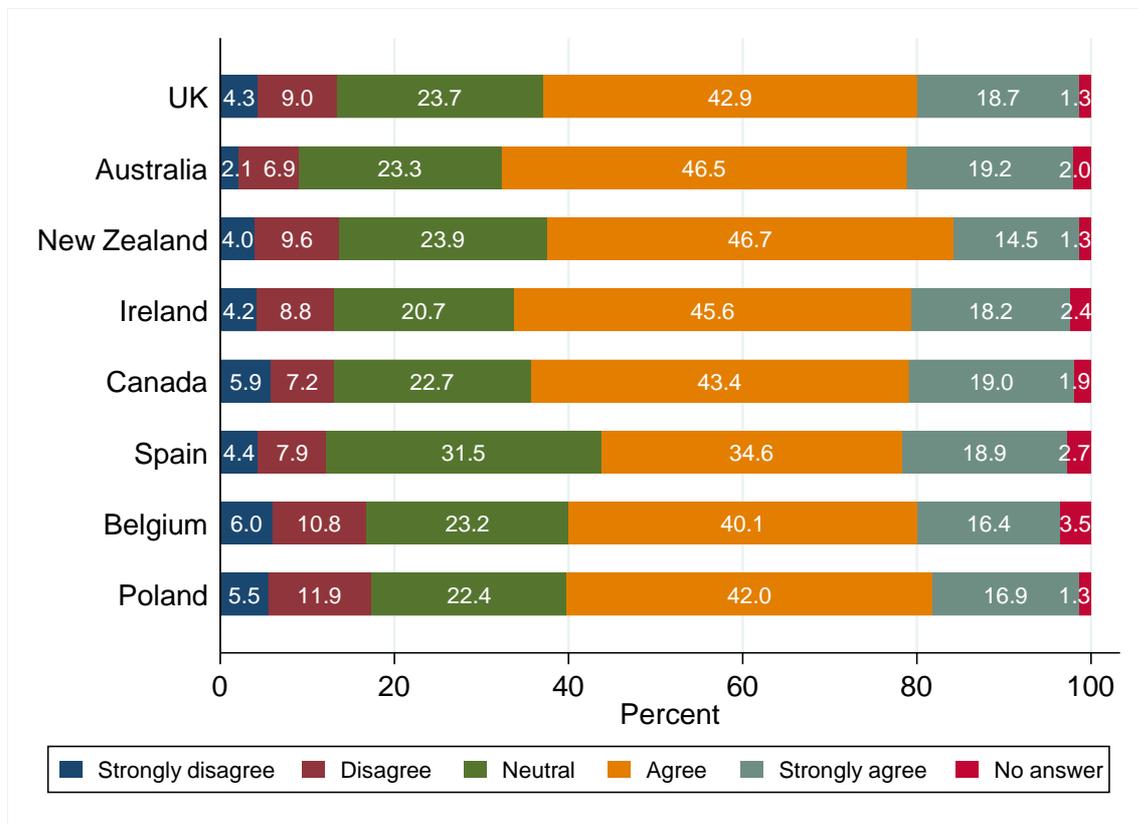
484

485 **Box 1: Consent options provided for primary care and Intensive Care Unit Comparative**

486 **Effectiveness Research scenarios**

For both low-risk scenarios, respondents were informed that 'information about the study would be circulated via newsletters, posters, and media outlets'.

Primary care CER scenario: comparison of two routinely used medications

- **Automatic enrolment:** You would be automatically included in the study. When being prescribed the medication, the doctor wouldn't mention the research.

- **Opt-out:** Sign me up automatically, but remind me of the study when I get the medicine and give me a chance to opt out. When being prescribed the medication, the doctor would give you more information and you would have a chance to opt out of the study if you-wished.

- **Opt-in:** Ask me to sign up when I am due to get the medicine. When being prescribed the medication, the doctor would explain the study and a researcher would ask you to sign up (prospective informed consent)

ICU CER scenario: comparison of two routinely available treatments
- **Deferred consent (family):** Include me immediately, family decides later if that's ok. You would be automatically included in the study. As soon as they could be contacted, a close family member would then decide whether or not you should stay included in the study.

- **Deferred consent (doctor):** Include me immediately, doctor decides later if that's ok. You would be immediately included in the study. A hospital doctor who is not a researcher in the study but who knew about it would decide whether or not you should stay included in the study.

- **Automatic enrolment:** Include me immediately, don't ask my or anyone's consent. You would be automatically included in the study without asking your consent or anyone consenting on your behalf.

- **Opt-in:** Don't include me until a family member says it's ok. You would not be included in the study until a close family member could be contacted to make that decision on your behalf (prospective informed consent provided by a third party if the patient lacks capacity)

487

Table 1: Demographic characteristics of the sample

Characteristic	UK (N=851)	Australia (N=851)	New Zealand (N=850)	Ireland (N=850)	Canada (N=851)	Spain (N=850)	Belgium (N=850)	Poland (N=851)	Overall (N=6804)
Age									
18-24	132 (15·51%)	105 (12·34%)	110 (12·94%)	117 (13·76%)	110 (12·93%)	92 (10·82%)	117 (13·76%)	133 (15·63%)	916 (13·46%)
25-34	181 (21·27%)	190 (22·33%)	165 (19·41%)	197 (23·18%)	173 (20·33%)	183 (21·53%)	172 (20·24%)	230 (27·03%)	1,491 (21·91%)
35-44	185 (21·74%)	197 (23·15%)	191 (22·47%)	208 (24·47%)	173 (20·33%)	221 (26·00%)	183 (21·53%)	196 (23·03%)	1,554 (22·84%)
45-54	179 (21·03%)	188 (22·09%)	201 (23·65%)	176 (20·71%)	213 (25·03%)	194 (22·82%)	196 (23·06%)	185 (21·74%)	1,532 (22·52%)
55-65 (55-59 Poland only)	174 (20·45%)	171 (20·09%)	183 (21·53%)	152 (17·88%)	182 (21·39%)	160 (18·82%)	182 (21·41%)	107 (12·57%)	1,311 (19·27%)
Gender									
Male	429 (50·41%)	422 (49·59%)	383 (45·06%)	407 (47·88%)	408 (47·94%)	425 (50·00%)	425 (50·00%)	428 (50·29%)	3,327 (48·90%)
Employment status:									
Employed full-time	444 (52·17%)	374 (43·95%)	374 (44·00%)	438 (51·53%)	496 (58·28%)	377 (44·35%)	420 (49·41%)	483 (56·76%)	3406 (50·06%)
Employed part-time	144 (16·92%)	166 (19·51%)	152 (17·88%)	80 (9·41%)	108 (12·69%)	83 (9·76%)	93 (10·94%)	70 (8·23%)	896 (13·17%)
Self-employed	58 (6·82%)	47 (5·52%)	84 (9·88%)	48 (5·65%)	70 (8·23%)	52 (6·12%)	35 (4·12%)	54 (6·35%)	448 (6·58%)
Unemployed, job seeking	34 (4·00%)	60 (7·05%)	58 (6·82%)	66 (7·76%)	39 (4·58%)	149 (17·53%)	53 (6·24%)	64 (7·52%)	523 (7·69%)
Unemployed not job seeking	82 (9·64%)	98 (11·52%)	95 (11·18%)	84 (9·88%)	61 (7·17%)	55 (6·47%)	95 (11·18%)	58 (6·82%)	628 (9·23%)
Retired	50 (5·88%)	58 (6·82%)	34 (4·00%)	46 (5·41%)	58 (6·82%)	39 (4·59%)	70 (8·24%)	40 (4·7%)	395 (5·81%)
Student / full- time education	30 (3·53%)	38 (4·47%)	44 (5·18%)	73 (8·59%)	13 (1·53%)	79 (9·29%)	71 (8·35%)	51 (5·99%)	399 (5·86%)
Other	9 (1·06%)	10 (1·18%)	9 (1·06%)	15 (1·76%)	6 (0·71%)	16 (1·88%)	13 (1·53%)	31 (3·64%)	109 (1·6%)
Education									
No completed education	3 (0·35%)	2 (0·24%)	6 (0·71%)	3 (0·35%)	2 (0·24%)	6 (0·71%)	15 (1·76%)	4 (0·47%)	41 (0·6%)
Primary education	4 (0·47%)	3 (0·35%)	3 (0·35%)	6 (0·71%)	0 (0%)	26 (3·06%)	12 (1·41%)	7 (0·82%)	61 (0·9%)
Lower secondary	168 (19·74%)	93 (10·93%)	92 (10··82%)	37 (4·35%)	19 (2·23%)	111 (13·06%)	93 (10·94%)	9 (1·06%)	622 (9·14%)
Upper secondary	254 (29·85%)	124 (14·57%)	126 (14·82%)	124 (14·59%)	143 (16·80%)	162 (19·06%)	270 (31·76%)	353 (41·48%)	1,556 (22·87%)
Post-secondary vocational	23 (2·7%)	263 (30·9%)	217 (25·53%)	162 (19·06%)	304 (35·72%)	127 (14·94%)	29 (3·41%)	91 (10·69%)	1,216 (17·87%)
Tertiary education	394 (46·30%)	360 (42·31%)	375 (44·11%)	510 (60%)	377 (44·30%)	410 (48·23%)	427 (50·24%)	378 (44·42%)	3231 (47·49%)
Prefer not to say	5 (0·59%)	6 (0·71%)	31 (3·65%)	8 (0·94%)	6 (0·71%)	8 (0·94%)	4 (0·47%)	9 (1·06%)	77 (1·13%)

Table 2: Factors predictive of willingness to participate in low and higher risk pandemic-relevant studies in primary care

Variable		Primary care low risk			Primary care high risk		
		OR	se	p	OR	se	p
Country				<0·0001			<0·0001
	UK	1·00	·	·	1·00	·	·
	Australia	0·90	0·12	0·441	1·15	0·13	0·217
	New Zealand	0·82	0·11	0·128	0·85	0·09	0·138
	Ireland	1·07	0·14	0·626	1·11	0·12	0·363
	Canada	0·69	0·09	0·005	0·85	0·09	0·138
	Spain	0·55***	0·07	<0·0001	0·77	0·08	0·016
	Belgium	0·44***	0·06	<0·0001	0·71**	0·08	0·002
	Poland	0·75	0·10	0·036	1·04	0·12	0·757
Age				0·3594			0·246
	18-24	1·00	·	·	1·00	·	·
	25-34	1·08	0·13	0·504	0·97	0·10	0·773
	35-44	1·20	0·15	0·133	1·17	0·12	0·131
	45-54	1·24	0·16	0·084	1·04	0·11	0·706
	55-65 (55-59 Poland only)	1·28	0·18	0·077	1·04	0·12	0·763
Gender							
	Male	1·00	·	·	1·00	·	·
	Female	1·05	0·07	0·468	0·79***	0·04	<0·0001
Working status							
	Working	1·00	·	·	1·00	·	·
	Not working	0·92	0·08	0·374	0·87	0·06	0·059
SES				0·264			0·989
	A	1·00	·	·	1·00	·	·
	B	1·17	0·14	0·200	1·04	0·10	0·725
	C1	1·01	0·12	0·939	1·00	0·10	0·996
	C2	0·98	0·13	0·873	0·99	0·11	0·913
	D	1·21	0·21	0·259	1·04	0·15	0·766
	E	0·93	0·13	0·611	1·04	0·13	0·747
Faith				0·061			0·334
	Muslim	0·55*	0·15	0·026	1·03	0·26	0·901
	Christian	1·00	·	·	1·00	·	·
	Jewish	0·56	0·23	0·159	0·58	0·21	0·124
	Hindu	1·19	0·45	0·653	1·19	0·36	0·566
	Buddhist	1·07	0·35	0·831	0·65	0·16	0·084
	Other	1·11	0·08	0·139	0·99	0·06	0·836
Education				0·158			0·749
	No completed education	1·00	·	·	1·00	·	·
	Primary education (ISCED 1)	0·63	0·31	0·343	0·69	0·31	0·406

Variable		Primary care low risk			Primary care high risk		
		OR	se	p	OR	se	p
	Lower secondary education (ISCED 2)	0·75	0·29	0·458	0·94	0·33	0·850
	Upper secondary education (ISCED 3)	0·81	0·31	0·574	0·92	0·32	0·810
	Post-secondary including pre-vocational or vocational education but not tertiary	0·91	0·35	0·814	0·88	0·31	0·704
	Tertiary education first level (ISCED 5)	0·99	0·38	0·974	0·84	0·29	0·616
	Tertiary education advanced level (ISCED 6)	1·08	0·50	0·868	1·03	0·42	0·940
Number of children in household				0·733			0·921
	None	1·00	·	·	1·00	·	·
	Only younger children	1·06	0·14	0·672	0·94	0·10	0·593
	Only older children	0·94	0·08	0·462	0·99	0·07	0·844
	Older and younger children	1·08	0·17	0·620	0·93	0·12	0·583
Marital status				0·268			0·036
	Single (never married)	1·00	·	·	1·00	·	·
	Living with partner	1·00	0·10	0·972	1·05	0·09	0·578
	Married /Civil partnership	0·93	0·09	0·456	1·01	0·08	0·899
	Separated	1·07	0·31	0·826	1·61	0·41	0·061
	Divorced	0·89	0·15	0·491	1·16	0·17	0·288
	Widowed	1·32	0·48	0·436	2·40**	0·75	0·005
	Prefer not to say	0·25	0·14	0·017	0·56	0·32	0·311
Knowledge about pandemics				<0·0001			< 0·0001
	Yes	1·00	·	·	1·00	·	·
	Just a little	0·92	0·08	0·294	0·80**	0·06	0·001
	No	0·59***	0·05	<0·0001	0·61***	0·05	<0·0001
ICU experience							
	No	1·00	·	·	1·00	·	·
	Yes	1·17	0·08	0·017	1·25***	0·07	<0·0001
Perceived health							
	Poor	1·00	·	·	1·00	·	·
	Good	1·07	0·09	0·439	1·11	0·08	0·131
Trust in GP				<0·0001			<0·0001
	Disagree	1·00	·	·	1·00	·	·
	Neutral	2·02***	0·24	<0·0001	1·67***	0·19	<0·0001
	Agree	3·18***	0·36	<0·0001	2·15***	0·23	<0·0001
Trust in government				<0·0001			<0·0001
	Low	1·00	·	·	1·00	·	·
	Neutral	1·74***	0·21	<0·0001	2·00***	0·24	<0·0001
	High	2·58***	0·35	<0·0001	3·10***	0·39	<0·0001
Therapeutic misconception				<0·0001			< 0·0001

Variable		Primary care low risk			Primary care high risk		
		OR	se	p	OR	se	p
	Low	1·00	·	·	1·00	·	·
	Neutral	2·54***	0·32	<0·0001	1·45**	0·18	0·003
	High	8·82***	1·18	<0·0001	2·72***	0·35	<0·0001
Access to new medication							0·0124
	Disagree				1·00	·	·
	Neutral				1·19	0·08	0·014
	Agree/				1·22**	0·09	0·005

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple ordinal regression models

Table 3: Consent preferences for inclusion in low risk study in primary care during an influenza pandemic

	First choice		Second choice		Third choice	
	All	Willing*	All	Willing	All	Willing
Automatic inclusion: "Include me automatically"	587 (8·63)	461 (9·78)	598 (8·79)	466 (9·88)	4404 (64·73)	3196 (67·78)
Opt-out: "Include me automatically, but remind me of the study when I get the medicine and give me a chance to opt out"·	1740 (25·57)	1371 (29·08)	4000 (58·79)	2841 (60·25)	317 (4·66)	232 (4·92)
Opt-in: "Only sign me up when I am due to get the medicine"·	3972 (58·38)	2742 (58·15)	1502 (22·07)	1169 (24·79)	724 (10·64)	602 (12·77)
No option preferred	505 (7·42)	141 (2·99)	704 (10·35)	239 (5·07)	1359 (19·97)	685 (14·53)

*Proportion of respondents who indicated "agree" or "strongly agree" when asked whether they would be willing to take part in he primary care low risk scenario (4715 of 6804, 69·3%)

Table 4: Factors predictive of willingness to engage with alternate consent models in low risk primary care including only participants who were "willing to take part"

Variable		OR	se	p
Country				0·006
	UK	1·00	·	·
	Australia	0·58	0·17	0·059
	New Zealand	0·78	0·25	0·441
	Ireland	1·53	0·55	0·231
	Canada	1·20	0·43	0·615
	Spain	0·54*	0·16	0·035
	Belgium	0·85	0·26	0·590
	Poland	1·59	0·58	0·205
Gender				
	Male	1·00	·	·
	Female	0·91	0·15	0·568
SES				0·006
	A	1·00	·	·
	B	1·00	0·33	0·995
	C1	0·88	0·29	0·702
	C2	0·71	0·25	0·331
	D	0·41*	0·15	0·013
	E	1·28	0·47	0·511
Education				0·290
	No completed education	1·00	·	·
	Primary education (ISCED 1)	0·72	0·69	0·735
	Lower secondary education (ISCED 2)	1·82	1·46	0·456
	Upper secondary education (ISCED 3)	2·00	1·56	0·377
	Post-secondary (incl. pre-vocational or vocational)	3·19	2·56	0·148
	Tertiary education – first level (ISCED 5)	2·03	1·58	0·363
	Tertiary education – advanced level (ISCED 6)	2·98	3·16	0·304
	Prefer not to say	1·30	1·70	0·839
ICU experience				
	No	1·00	·	·
	Yes	1·85***	0·32	<0·001
Illness experience				
	No	1·00	·	·
	Yes	0·73	0·20	0·254
Number of children in household				0·993
	0	1·00	·	·
	1	1·06	0·23	0·980
	2	0·98	0·24	0·942
	3 +	0·98	0·0·34	0·948
Faith				0·219
	Muslim	0·34*	0·17	0·033

Variable		OR	se	p
	Christian	1·00	·	·
	Jewish	0·57	0·60	0·593
	Hindu	1·80	1·86	0·571
	Other	1·08	0·18	0·659
Knowledge of pandemics				0·011
	A great deal/ fair amount	1·00	·	·
	Just a little	0·89	0·19	0·595
	Hear of but know nothing about/ never heard of	0·55**	0·13	0·009
Trust in government				<0·001
	Low	1·00	·	·
	Neutral	3·52***	1·02	<0·001
	High	3·17***	0·97	<0·001
Therapeutic misconception				0·782
	Low	1·00	·	·
	Neutral	1·37	0·62	0·493
	High	1·29	0·58	0·571

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple logistic regression model

Table 5: Factors predictive of willingness to participate in low and higher risk pandemic-relevant studies in ICU

Variable		ICU low risk			ICU high risk		
		OR	se	p	OR	se	p
Country				<0·0001			<0·0001
	UK	1·00	·	·	1·00	·	·
	Australia	1·22	0·16	0·125	1·12	0·13	0·364
	New Zealand	0·98	0·13	0·863	1·02	0·12	0·877
	Ireland	1·30*	0·17	0·047	1·19	0·14	0·152
	Canada	0·85	0·11	0·209	0·99	0·12	0·923
	Spain	0·68**	0·09	0·003	0·58***	0·07	<0·0001
	Belgium	0·77*	0·10	0·043	0·74*	0·09	0·012
	Poland	0·89	0·12	0·392	0·76*	0·10	0·028
Age				0·117			0·013
	18-24	1·00	·	·	1·00	·	·
	25-34	1·24	0·14	0·069	1·07	0·12	0·547
	35-44	1·18	0·14	0·159	1·33*	0·15	0·011
	45-54	1·30*	0·16	0·036	1·36**	0·16	0·008
	55-65 (55-59 Poland only)	1·06	0·15	0·660	1·37*	0·17	0·013
Gender							
	Male	1·00	·	·	1·00	·	·
	Female	0·93	0·06	0·254	0·95	0·06	0·407
Working status							
	Working	1·00	·	·	1·00	·	·
	Not working	0·98	0·09	0·801	1·01	0·08	0·906
SES				0·0181			0·0786
	A	1·00	·	·	1·00	·	·
	B	1·31*	0·16	0·021	1·30*	0·14	0·015
	C1	1·17	0·14	0·195	1·15	0·13	0·198
	C2	1·05	0·14	0·693	1·15	0·14	0·235
	D	1·07	0·17	0·690	1·17	0·18	0·305
	E	0·87	0·12	0·343	0·97	0·13	0·810
Faith				0·223			0·013
	Muslim	0·76	0·22	0·340	0·59*	0·15	0·042
	Christian	1·00	·	·	1·00	·	·
	Jewish	0·48	0·18	0·056	0·54	0·22	0·128
	Hindu	0·66	0·21	0·197	0·76	0·25	0·405
	Buddhist	0·72	0·22	0·279	0·60	0·17	0·063
	Other	0·98	0·07	0·731	1·10	0·07	0·134
Education				0·131			0·090
	No completed education	1·00	·	·	1·00	·	·
	Primary education (ISCED 1)	0·71	0·34	0·482	0·47	0·22	0·099

Variable	ICU low risk			ICU high risk		
	OR	se	p	OR	se	p
Lower secondary education (ISCED 2)	0·97	0·37	0·939	0·90	0·33	0·773
Upper secondary education (ISCED 3)	0·79	0·30	0·525	0·78	0·28	0·492
Post-secondary including pre-vocational or vocational education but not tertiary	0·89	0·34	0·769	0·78	0·28	0·500
Tertiary education first level (ISCED 5)	1·01	0·38	0·970	0·92	0·33	0·812
Tertiary education advanced level (ISCED 6)	1·04	0·47	0·939	1·10	0·48	0·817
Number of children in household			0·401			0·3586
None	1·00	·	·	1·00	·	·
Only younger children	0·83	0·10	0·128	0·84	0·10	0·145
Only older children	0·92	0·08	0·347	0·98	0·08	0·822
Older and younger children	0·87	0·13	0·358	0·84	0·12	0·206
Marital status			0·396			0·1500
Single (never married)	1·00	·	·	1·00	·	·
Living with partner	0·89	0·09	0·274	0·91	0·09	0·336
Married /Civil partnership	1·06	0·10	0·545	0·94	0·08	0·500
Separated	1·52	0·48	0·189	1·20	0·33	0·512
Divorced	1·16	0·19	0·380	1·13	0·18	0·453
Widowed	1·46	0·51	0·275	1·81	0·61	0·078
Prefer not to say	0·88	0·56	0·844	0·37	0·21	0·077
Knowledge about pandemics			<0·0001			<0·0001
Yes	1·00	·	·	1·00	·	·
Just a little	0·86	0·07	0·0560	0·74***	0·06	0·0001
No	0·60***	0·06	<0·0001	0·55***	0·05	<0·0001
ICU experience						
No	1·00	·	·	1·00	·	·
Yes	1·16	0·08	0·024	1·20**	0·07	0·003
Perceived health						
Poor	1·00	·	·	1·00	·	·
Good	0·97	0·08	0·699	1·26**	0·10	0·002
Trust in GP			<0·0001			<0·0001
Disagree	1·00	·	·	1·00	·	·
Neutral	1·34**	0·16	0·016	1·63***	0·20	<0·0001
Agree	1·76***	0·20	<0·0001	2·27***	0·25	<0·0001
Trust in government			<0·0001			<0·0001
Low	1·00	·	·	1·00	·	·
Neutral	2·21***	0·27	<0·0001	2·66***	0·32	<0·0001
High	3·72***	0·50	<0·0001	4·06***	0·53	<0·0001
Therapeutic misconception			<0·0001			<0·0001
Low	1·00	·	·	1·00	·	·

Variable	ICU low risk			ICU high risk		
	OR	se	p	OR	se	p
Neutral	1·74***	0·22	<0·0001	0·95	0·12	0·680
High	4·35***	0·59	<0·0001	1·58***	0·21	0·001
Access to new medication						<0·0001
Disagree				1·00	·	·
Neutral				1·48***	0·11	<0·0001
Agree/				4·85***	0·41	<0·0001

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple ordinal logistic regression models

Table 6: Consent preferences for inclusion in low risk study in ICU during an influenza pandemic

	First choice		Second choice		Third choice		Fourth choice	
	All	Willing*	All	Willing	All	Willing	All	Willing
Deferred consent (family) Include me immediately, family decides later if that's ok	1163 (17·09)	958 (20·04)	2236 32·86)	1690 (35·36)	1620 (23·81)	1223 (25·59)	741 (10·89)	499 (10·44)
Deferred consent (doctor): Include me immediately, doctor decides later if that's ok	1637 (24·06)	1343 (28·09)	2077 (30·53)	1582 (33·10)	1809 (27·78)	1266 (26·49)	294 (4·32)	221 (4·62)
Automatic enrolment: Include me immediately, don't ask my or anyone's consent	718 (10·55)	592 (12·38)	945 (13·89)	724 (15·15)	1269 (18·65)	995 (20·82)	2649 (38·93)	1945 (40·69)
Opt-in: Don't include me until a family member says it's ok	2623 (38·55)	1686 (35·27)	621 (9·13)	458 (9·58)	1056 (15·52)	884 (18·49)	1576 (23·16)	1344 (28·12)
No preference recorded	663 (9·74	201 (4·21)	925 (13·59)	326 (6·82)	1050 (15·43)	412 (8·62)	1544 (22·69)	771 (16·13)

*Proportion of respondents who indicated "agree" or "strongly agree" when asked whether they would be willing to take

part in the primary care low risk scenario

Table 7 Binary logistic regression of participant consent preferences for low risk ICU study during an influenza

pandemic including only participants who were willing to participate

Variable		OR	se	p
Country				0·004
	UK	1·00	·	·
	Australia	1·25	0·33	0·399
	New Zealand	1·47	0·42	0·185
	Ireland	2·67**	0·86	0·002
	Canada	1·16	0·32	0·583
	Spain	0·83	0·21	0·478
	Belgium	0·74	0·18	0·205
	Poland	1·27	0·34	0·368
Age				0·580
	18-24	1·00	·	·
	25-34	0·86	0·21	0·525
	35-44	0·80	0·21	0·391
	45-54	1·06	0·28	0·832
	55-65 (55-59 Poland only)	0·77	0·21	0·347
Gender				
	Male	1·00	·	·
	Female	0·69**	0·10	0·008
SES				0·024
	A	1·00	·	·
	B	1·08	0·29	0·763
	C1	0·85	0·22	0·538
	C2	0·71	0·20	0·223
	D	0·81	0·28	0·536
	E	1·74	0·57	0·085
Education				0·013
	No completed education	1·00	·	·
	Primary education (ISCED 1)	0·60	0·51	0·550
	Lower secondary education (ISCED 2)	2·19	1·49	0·250
	Upper secondary education (ISCED 3)	2·28	1·50	0·210
	Post-secondary including pre-vocational or vocational education but not tertiary	2·50	0·1·68	0·173
	Tertiary education – first level (ISCED 5)	1·88	1·22	0·173
	Tertiary education – advanced level (ISCED 6)	0·85	0·64	0·834
	Prefer not to say	0·45	0·41	0·385
ICU Experience				
	No	1·00	·	·
	Yes	2·00**	0·29	<0·001
Illness Experience				
	No	1·00	·	·
	Yes	0·85	0·21	0·524
Perceived health				
	Poor	1·00	·	·
	Good	1·13	0·20	0·492
Number of people in household				0·693

Variable		OR	se	p
	1	1·00	·	·
	2	0·66	0·17	0·109
	3	0·74	0·21	0·296
	4	0·72	0·22	0·280
	5	0·65	0·25	0·270
	6	1·21	0·80	0·769
	7	1·39	1·49	0·760
			·	·
Number of children				0·972
	0	1·00	·	·
	1	0·92	0·19	0·676
	2	0·97	0·27	0·918
	3 +	1·05	0·45	0·906
Marital status				
	On their own	1·00	·	·
	Living with someone	1·68**	0·29	0·003
Knowledge of pandemics				0·248
	A great deal/ fair amount	1·00	·	·
	Just a little	0·97	0·17	0·875
	Hear of but know nothing about/ never heard of	0·76	0·15	0·154
Trust in government				0·003
	Low	1·00	·	·
	Neutral	2·33**	0·62	0·001
	High	2·54*	0·71	0·001
Therapeutic misconception				0·479
	Low	1·00	·	·
	Neutral	1·36	0·45	0·356
	High	1·47	0·48	0·238

3

4 Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

5 Estimates obtained from multiple logistic regression model

6

Table 8: Factors predictive of willingness to donate excess from clinical samples for pandemic-relevant research

		Overall		
		OR	se	p
Country				<0·001
	UK	1·00	·	·
	Australia	0·66	0·10	0·004
	New Zealand	0·69*	0·10	0·012
	Ireland	0·83	0·12	0·201
	Canada	0·69*	0·10	0·014
	Spain	0·46***	0·07	<0·001
	Belgium	0·71*	0·11	0·024
	Poland	0·48***	0·07	<0·001
Age				<0·001
	18-24	1·00	·	·
	25-34	1·34*	0·16	0·011
	35-44	1·55***	0·18	<0·001
	45-54	1·98***	0·24	<0·001
	55-65 (55-59 Poland only)	2·29***	0·31	<0·001
Gender				
	Male	1·00	·	·
	Female	1·04	0·07	0·585
Employment status				
	Working	1·00	·	·
	Not working	1·07	0·10	0·488
SES				0·0024
	A	1·00	·	·
	B	1·23	0·16	0·127
	C1	1·05	0·14	0·705
	C2	0·81	0·11	0·142
	D	0·81	0·14	0·208
	E	0·83	0·13	0·217
Faith				0·0204
	Muslim	0·59	0·17	0·063
	Christian	1·00	·	·
	Jewish	1·19	0·61	0·731
	Hindu	0·57	0·18	0·082
	Buddhist	0·92	0·30	0·801
	Other	1·18*	0·09	0·033
Knowledge about pandemics				<0·001
	A great deal/ fair amount	1·00	·	·
	Just a little	0·96	0·09	0·625
	Hear of but know nothing about/ never heard of	0·70***	0·07	<0·001
ICU Experience				
	No	1·00	·	·
	Yes	1·34	0·10	<0·001
Perceived overall health				
	Poor	1·00	·	·
	Good	1·15	0·10	0·106

		OR	se	p
Trust in GP				<0·001
	Strongly disagree/disagree	1·00	·	·
	Neutral	1·10	0·14	0·472
	Agree/strongly agree	1·95***	0·24	<0·001
Trust in government				<0·001
	Low	1·00	·	·
	Neutral	2·40***	0·31	<0·001
	High	4·84***	0·71	<0·001
Therapeutic misconception				<0·001
	Low	1·00	·	·
	Neutral	1·00	0·15	0·989
	High	1·60**	0·25	0·002

8

9   Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001