



Recommendations for the inclusion and study of sex and gender in research

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1 Recommendations for the Inclusion and Study of Sex and Gender in Research

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39

40 **Abstract**

41 Sex and gender are important variables in research but are inconsistently explored. The international
42 PAINDIFF Network make thirteen recommendations for studying sex and gender as variables in pain
43 research, which are applicable across the spectrum of biopsychosocial research. Five universal
44 recommendations apply to the majority of research studies: 1) Include males and females as standard
45 practice, 2) Account for sex in randomization/counterbalancing and testing order, 3) Power for sex
46 differences when sex is a primary experimental variable, 4) Include detailed reporting of experimental
47 design and 5) Conduct sex disaggregated analysis and reporting. Three additional recommendations
48 specifically for preclinical studies and five additional recommendations for human/clinical studies are
49 included. Recommendations for stakeholders such as editors, reviewers, funding bodies and policy
50 makers have also been developed. Wide adoption and implementation of these recommendations
51 will reduce variability, improve reproducibility, and enhance translatability of research findings within
52 and beyond the field of pain.

53

54 **Introduction**

55 There has been a rapid change in the approach of healthcare professionals towards more personalized
56 health care over the past 10 years. This approach acknowledges that key health outcomes - morbidity,
57 response to treatment, prognosis - are influenced by individual variability at the molecular, cellular,
58 physiological, systems, psychological, and social levels. Increased awareness of the importance of sex
59 and gender (see Box 1 for definitions) as key individual difference variables that contribute to health
60 and disease, together with requirements of many funding agencies and encouragement from scientific
61 journals¹⁻⁴, has resulted in profound increases in the number of studies investigating sex and/or
62 gender differences across the biopsychosocial sciences. This welcome development has resulted in
63 mounting evidence for differences in pathophysiology and experience of pain between and across
64 sexes and genders (for recent reviews see⁵⁻¹²). At this time of rapid acceleration in the number and
65 scope of studies in which sex and gender are incorporated as variables, the biopsychosocial research
66 community must adopt consistent research approaches to maximize progress in this critically
67 important area.

68 Several guidelines and recommendations have been published in recent years calling for the inclusion
69 of sex and/or gender as variables across various disciplines (for example see¹³⁻²¹). However, the vast
70 majority have been of limited scope in that they focused on recommendations that pertain to either
71 preclinical or human/clinical research but not both, have focused on specific aspects of experimental
72 design, analysis and/or reporting (but rarely all three) or have not included data on current opinions
73 and practices by researchers in the field. In this Perspective, we make recommendations on best
74 practice methodological approaches for the inclusion, study and reporting of sex and gender as
75 variables in preclinical and human/clinical pain research. We also provide recommendations for key
76 stakeholders such as editors, reviewers, funding bodies and policy makers to ensure widespread
77 recognition, acknowledgement and support of best practice in the field.

78 **Current recommendations for examining sex and gender differences in pain research**

79 The field of pain has been at the leading edge of research on sex and gender and in 2007, the
80 International Association for the Study of Pain (IASP) Special Interest Group on Sex, Gender and Pain
81 developed a consensus report for investigating sex and gender differences in pain and analgesia²².
82 Although this has been a key resource, the uptake of these recommendations has been limited²³⁻²⁵,
83 and the landscape for studying sex and gender has expanded significantly since 2007. Accordingly, in

84 2024, the IASP Global Year awareness campaign was designated for “Sex and Gender Disparities in
85 Pain” (see²⁶⁻²⁸ and ²⁹ for associated publications). Several publications have recommended
86 incorporating sex and gender as key factors in study design, including as potential covariates or
87 variables to evaluate when statistical power permits^{6,25,30,31}. However, despite these good efforts,
88 these works have largely failed to provide guidelines on when and how to apply such considerations.
89 Recently, Keogh and Boerner reported on five key challenges to incorporating sex and gender into
90 pain research: conceptual impressions, research bias, binary limitations, challenges with integrating
91 sex and gender, and moving from observation to advocacy and meaningful change³². Their work
92 provided a valuable update, particularly for the clinical pain research community. However, several
93 questions remain, as does the need to review and develop further guidelines to ensure best practice
94 approaches for the inclusion and study of basic/preclinical, clinical and translational pain research.

95 In the clinical domain, there is a need to move beyond an over-reliance on binary category comparison
96 to fully understand how and why pain is impacted by sex and gender. Sex is typically regarded as a
97 biological concept and gender as a socio-psychological concept (see Box 1), but they also overlap and
98 can be considered as interacting factors. Little is known about the experience of pain in individuals
99 with variations of sex traits, or those with diverse gender identities (e.g., transgender, gender fluid,
100 non-binary), but emerging data suggests an important role of minority stressors, gender biases and
101 unique experiences (e.g., pain associated with gender-affirming medical and social practices) on pain
102 , and this necessitates further study^{7,12,33,34}. Thus, guidance on how best to incorporate, analyse and
103 report the diversity of sex and gender in human/clinical research is warranted. In preclinical studies
104 that use laboratory animals, it is well-recognised that replication across laboratories is challenging, if
105 not impossible in some cases³⁵, despite the fact that quantitative and mechanistic sex differences in
106 nociceptive and affective pain responses continue to be uncovered.

107 To address these challenges, the PAINDIFF Network expert group was established and supported by
108 ERA-NET NEURON, a Network of European Funding for Neuroscience Research ([https://www.neuron-](https://www.neuron-eranet.eu)
109 [eranet.eu](https://www.neuron-eranet.eu)). The PAINDIFF Network comprised 32 individuals (16 female and 16 male) including early
110 career, mid-career, and senior researchers, and patient advocates, from 22 institutions across 8
111 countries. Network members were invited to participate by the PAINDIFF lead investigators who are
112 experienced pain researchers. Research expertise within the Network spans basic science, clinical and
113 translational pain research. Several of the Network members were co-authors of the two previous
114 publications regarding recommendations on the study of sex and gender in pain research^{22,32} [S.L,
115 E.A.M, J.S.M., E.K. & K.E.B.]. The Network sought to make recommendations on methodological
116 approaches for best practice in the study and reporting of sex and gender as variables in pain research
117 (basic/preclinical and/or human/clinical research). The recommendations are broadly applicable
118 across the spectrum of biopsychosocial research. Adoption and implementation of these
119 recommendations could decrease the variability of findings and improve reproducibility between
120 laboratories and clinical settings, thereby improving the translatability of research findings within and
121 beyond pain, ultimately leading to better and more equitable treatment outcomes.

122

123 **Methodological approach to achieve recommendations and guidelines**

124 We developed recommendations and guidelines based on the findings from three methodological
125 approaches: (i) a literature review on guidelines and recommendations for the inclusion and study of
126 sex and gender differences in pain research, (ii) an international cross-sectional survey of pain
127 researchers on current practices and opinions in the field, informed by the literature review, and (iii)

128 multi-disciplinary network meetings, discussion and consensus. Sex and gender were defined in
129 accordance with international guidelines (see Box 1).

130

131 **Literature Review**

132 We conducted a literature review to examine current practice and guidelines for the study of sex and
133 gender in preclinical and human/clinical research with a particular focus on pain. Manuscript titles
134 were searched for the following terms (Sex OR Gender) AND Pain AND either Guidelines,
135 Recommendations, Consensus, Experimental design, Method* OR Reporting. Databases (Pubmed,
136 Google Scholar and Scopus), and abstracts screened for recommendations, challenges or guidelines.
137 Searches took place over the period of March – December 2024, and July 2025, with no constraints
138 applied to the date of publication.

139

140 **Cross-Sectional International Survey**

141 We launched a cross-sectional survey of international pain researchers via the Qualtrics survey
142 platform on two occasions from 29th March to 22nd April 2024, and from 1st to 14th June 2024. Ethical
143 approval was obtained from the University of Galway's Research Ethics Committee (ID no.
144 2024.01.013). The survey comprised 99 questions in the English language that examined current
145 practice in, and opinion on, methodological approaches to the study of sex and gender as variables in
146 preclinical pain research (non-human animals, cells or tissues) and human/clinical research (humans,
147 and/ or cells, tissues or fluids derived from humans, e.g. iPSCs, biopsies, plasma etc.). The survey
148 questions were informed by our review of the literature and discussion among PAINDIFF network
149 members. Of the 99 questions, 38 addressed preclinical research, 43 addressed human/clinical
150 research, and 18 questions were related to the demographics of the survey respondents, and
151 perceived barriers and enablers of sex/gender research. Participants were invited to complete the
152 preclinical and/or human/clinical arms of the survey, depending on their area(s) of research. The
153 survey was advertised on the PAINDIFF website (<https://www.paindiff.com/survey>) and conveyed via
154 European Pain Federation (EFIC) and International Association for the Study of Pain (IASP)
155 communications channels, partner networks, and by word of mouth. Survey questions were a mix of
156 multiple-choice and short-answer questions allowing free-text/open-ended responses (See survey
157 questions in Supplementary Data S1).

158

159 **PAINDIFF Network Meetings**

160 The Network was launched in September 2023 during the EFIC Pain in Europe Congress in Budapest,
161 Hungary with a hybrid meeting of the partners followed by a series of online subgroup meetings that
162 focused on developing the survey questions. A half-day online meeting of the partners took place in
163 January 2024 to review the potential survey questions and to plan the launch of the survey. After the
164 initial survey was closed in April, a 2-day hybrid Network meeting took place in May 2024 in Galway,
165 Ireland to discuss the results of the survey. Network members were invited to propose
166 recommendations based on key findings and considerations and to contribute to refinement of draft
167 recommendations. Based on the interim survey analysis, it was decided to relaunch the survey to
168 capture more responses from geographically diverse populations. A subsequent hybrid meeting of the
169 partners took place during the IASP World Pain Congress in August 2024 in Amsterdam, The
170 Netherlands to discuss final survey results and achieve consensus on recommendations. The Chatham

171 House rule (<https://www.chathamhouse.org/about-us/chatham-house-rule>) was used to encourage
172 open and free discussion and protect the anonymity of the attendees. Decisions were reached by
173 consensus at each stage; for the network's purpose, consensus was defined as assent of each PAINDIFF
174 partner to wording and intent of the recommendation and disagreement of none³⁶. Two weeks in
175 advance of the August 2024 meeting, the draft recommendations generated at the May 2024 meeting
176 were shared with network members via Sharepoint and email for the purpose of considering their
177 inclusion and refinement. Each member was invited to propose written amendments in advance of
178 the August meeting (as individuals) or at the meeting itself (in a collective setting). Written and verbal
179 responses were addressed at the meeting and the Chair sought assent to inclusion and wording of
180 each final recommendation. The final recommendation regarding the reporting and analysis of sex-
181 disaggregated data was agreed to by all only after detailed discussion of its value and consideration
182 of several forms of wording. At no point was there disagreement or dissent that warranted voting.

183

184 **Statistical analysis and data reporting of the survey findings**

185 Quantitative analysis of survey data consisted of descriptive statistics of multiple-choice question
186 responses (See Supplementary Table S1-S4). We also used Chi-square tests of independence to
187 examine associations between participants' survey responses and categorical variables, because all
188 variables of interest were categorical. The analyses were carried out separately for two subsections of
189 the dataset: the participants who completed the preclinical survey and those participants who
190 completed the clinical survey. We used an inclusive approach so that participants who completed both
191 surveys were included in each respective analysis. The analyses were conducted using the statistical
192 programming language R (<https://www.R-project.org/>), with Chi-square tests computed using the
193 "jmv" package (<https://cran.r-project.org/package=jmv>).

194 The associations between answers to each survey question and the following 6 factors were
195 computed: (i) Survey completion status: Completed vs. Non-Completed; (ii) Principal investigator (PI)
196 status: PI vs. Non-PI; (iii) Sex: Female vs. Male; iv) Gender: Men vs Women (it was not possible to
197 perform an analysis of sex and gender beyond the binary of male/men and female/women due to the
198 small number of individuals [sub-samples ranging from n = 1-4] in non-binary categories). However,
199 data for all sex and gender categories are provided in Supplementary Tables S3 and S4); (v) Country
200 income level: High-Income vs. Middle/Low-Income, as classified by the Wellcome³⁷ (vi) Career stage:
201 Graduate Student (e.g., MSc, PhD) vs. Early Career Researcher (<10 years since final degree, e.g.,
202 Postdoctoral Fellow, Independent Investigator) vs. Mid-Career Researcher (10–20 years since final
203 degree) vs. Advanced Career Researcher (>20 years since final degree). Additionally, Chi-square tests
204 of independence were used to assess differences in survey responses between participants who
205 completed both surveys and those who completed only one survey. Due to the number of tests
206 conducted, post-hoc corrections were applied using the Benjamini-Hochberg (BH) procedure. The BH
207 procedure controls the false discovery rate, which is the expected proportion of false positives (Type
208 I errors) among the significant results in multiple comparisons³⁸. Controlling Type I errors while
209 allowing for the identification of potentially significant associations was prioritised.

210 Qualitative content analysis of the text responses was conducted, and coded by two investigators
211 (F.S. and K.E.B.) into categories for each question³⁹.

212

213 **Outcomes**

214 The literature review identified 31 articles published between 1996 and 2025 relating to
215 methodological approaches to the study of sex or gender in pain. Abstracts of all articles were scanned
216 and four manuscripts that included recommendations or guidelines were identified^{22,30-32}. Of these,
217 only two articles proposed detailed recommendations and challenges for the study of both sex and
218 gender differences in pain research^{22,32}. The first, while very important and influential, is now over 17
219 years old, whereas the latter focused mostly on conceptual challenges and pertained primarily to
220 human/clinical research. Thus, there is a need for further guidelines and recommendations for all
221 types of studies of pain, in animal models and humans, that consider present day needs and culture.

222 The current survey was undertaken by 483 pain researchers across the world, with representation
223 across sexes, genders, disciplines and career stages (see Figure 1 and Supplementary Table S1).
224 Although most (60-90%) preclinical and human/clinical pain respondents consider *sex* as a variable in
225 the design, analysis, reporting and interpretation of their studies, most human/clinical pain
226 researchers (over 50%) rarely or never consider *gender* in these elements of their research (Figure 2;
227 Supplementary Table S2). Analysis revealed that none of the associations between answers to each
228 survey question and the 6 factors examined were found to be significant for any of the quantitative
229 survey data. Free text/open-ended responses provided additional context and information on the
230 practices of pain researchers concerning the incorporation of sex and gender in their studies, examples
231 of which are provided in *italics* below and in Figure 3.

232 The outcomes of the literature review and survey data informed the discussion of the Network group,
233 which agreed by consensus a set of universal recommendations that could be applied to both
234 preclinical and clinical research (described in list below and see Figure 4). Additional recommendations
235 outside these that pertain specifically to either preclinical (PC1-3) or human/clinical (H/C1-5) research
236 were also developed.

237

238 **1. Universal recommendations for both preclinical and human/clinical studies**

239 It is challenging to generate universal recommendations given that researchers need to consider what
240 is appropriate within the context of their specific studies. For example, sex and/or gender
241 considerations are dependent on the population, hypothesis and question(s) under study. With this in
242 mind, we put forth five recommendations that pertain to *the majority of* studies and thus focus on sex
243 rather than gender, because sex is relevant to both preclinical and human/clinical research, whereas
244 gender is largely relevant only to human/clinical research. While acknowledging that there is a need
245 for research specifically on variations of sex traits, the universal recommendations outlined below
246 reflect the common use of the binary male vs. female in preclinical studies.

247

248 **Universal Recommendation 1: Include males and females as standard practice unless there is a valid**
249 **reason not to do so.**

250 Although most (>75%) preclinical survey respondents consider sex as a variable in the design, analysis,
251 reporting and interpretation of their research, only 40% of preclinical respondents include both males
252 and females in the majority of their research (Figure 2; Supplementary Table S2), which is in line with
253 recent meta-analyses in the field^{25,40}. By comparison, most (68%) human/clinical researchers include
254 both males and females in their research studies, however only 33% of human/clinical researchers
255 always analyse for sex differences, consistent with published data²⁵ (Figure 2; Supplementary Table
256 S2). Thus, while recognising the importance of the study of sex as a variable in pain, most researchers

257 still do not routinely include this in their own practice. The most common reasons for not carrying out
258 pain-related research in more than one sex included *relevance to the research questions, lack of*
259 *resources* and *small sample size* (Figure 3). Preclinically, respondents often cited *increased variability*
260 as a reason for not using females in their research, despite several studies demonstrating that data
261 from female rodents are not more variable than data from males⁴¹⁻⁴³. There are limited valid reasons
262 for not including both males and females in research studies such as if the pain condition (e.g. vaginal
263 or penile pain) or an underlying mechanism under investigation is relevant to only one sex. In studies
264 where only one sex is used, the reason for doing so should be stated explicitly.

265

266 **Universal Recommendation 2: Account for sex in randomization/counterbalancing/testing order**

267 The experimental design of preclinical animal studies using both sexes is not standardised; a finding
268 reflected in the survey responses. For example, 36% of survey respondents reported using both sexes
269 in each study test session, batch, or cohort for behavioural experiments; 28% including one sex only
270 in each test session/batch/cohort; 21% carrying out the study in one sex in the first instance
271 (Supplementary Table S2 Q24). By comparison, most (58%) respondents to the human/clinical survey
272 report including both male and female participants in each study test session/batch/cohort
273 (Supplementary Table S2 Q24). Our recommendation for best practice is that where possible,
274 preclinical and human/clinical studies should be designed such that males and females are tested in
275 parallel within the same study (and within each batch or cohort for studies where there may be
276 multiple batches or cohorts), and in a randomised or counter-balanced manner, to control for
277 potential differential effects of variables (e.g. order of testing, time of day or year, different
278 experimenters, training effects) on both sexes. This is particularly important for studies where the aim
279 is to make direct statistical comparisons between males and females. We acknowledge that
280 implementation of this recommendation may not be possible in all studies or all study types (e.g.,
281 epidemiological studies). In study types for which randomisation is possible but not employed,
282 justification for why it was not employed should be provided.

283

284 **Universal Recommendation 3: Use adequately powered study design to detect sex differences when** 285 **it is the primary experimental variable or when data suggest sex-specific effects**

286 Although most (62-74%) respondents to the PAINDIFF survey indicated that they sometimes or always
287 consider sex differences when calculating sample size, preclinical pain researchers are more likely to
288 power for sex differences (Supplementary Table S2 Q43) whereas human/clinical researchers are
289 more likely to combine different sexes into the same group (Supplementary Table S2 Q79). We
290 recommend that if the investigation of sex differences is the primary experimental aim, or where prior
291 data suggest sex-specific effects, the study should be adequately powered to detect such
292 differences/effects if they exist. However, it is not always necessary to power studies for sex
293 differences (e.g. where this is not the primary experimental aim). In cases where the study of sex
294 differences is not the primary experimental aim, both male and female sexes should nevertheless be
295 included in the study design. Unless the aim is to specifically compare male vs female, those identifying
296 as intersex, or who prefer not to identify, should not be excluded but rather should be included in the
297 study and reported on (e.g., in tables, supplementary materials). Researchers are encouraged to
298 consider conducting secondary analysis to assess sex as a variable and/or calculate the power required
299 to inform experimental design for future studies that might pursue evaluation of sex differences
300 (see^{18,44}).

301

302 **Universal Recommendation 4: Include detailed reporting of experimental design including sex of**
303 **the experimenter when possible**

304 Given there is a wide variety of practices employed across and within research settings (see
305 Supplementary Table S2), it is not possible to recommend a single standardised approach to
306 experimental design with consideration of sex. However, it is recommended to record and report the
307 following in sufficient detail to allow other researchers interested in sex as a variable to be able to
308 replicate the experiment and/or collate data for pooled analyses: experimental design, environmental
309 conditions, order of testing, and (when possible) the sex of the experimenter who interacted with the
310 experimental subjects/participants. Increasing evidence indicates that the sex of the experimenter can
311 influence pain responding and outcomes of experimental subjects/participants in both preclinical and
312 human/clinical studies⁴⁵⁻⁴⁹. We recognise and acknowledge that some experimenters may be
313 uncomfortable or unwilling to declare their sex. Thus, we recommend that authors consider such
314 declarations, treat as optional, and the handling and storage of such data should comply with any
315 relevant data protection/privacy regulations in force within the relevant jurisdiction.

316

317 **Universal Recommendation 5: Conduct sex-disaggregated analysis and reporting**

318 Although both sexes are commonly included in human/clinical pain research, the literature indicates
319 that less than 20% of studies published in one of the leading pain journals (PAIN) over the period 2012
320 to 2021 analysed for, or reported on, the effect of sex²⁵. By comparison, data from the PAINDIFF survey
321 indicate that 81% and 74% of respondents sometimes or always analyse and report on sex differences
322 in their preclinical and human/clinical research respectively, which may mean that this practice in the
323 field is changing. Sex-disaggregated analysis and reporting should be considered as standard,
324 irrespective of whether the data are also presented as pooled across sex, or whether there are
325 significant differences, and the raw sex-disaggregated data should be made available publicly. The
326 analysis could take the form of inferential statistics to investigate both within- and between-sex
327 effects (where this is a primary aim for which the experiment has been adequately powered).
328 Alternatively, for more exploratory studies or those where the detection of sex effects is not the
329 primary aim, the analysis could take the form of sample size/power calculations to inform the design
330 of future studies aimed at investigating the effects of sex.

331

332 Universal recommendations 1-5 apply to the inclusion and study of sex in preclinical research and sex
333 and gender in human/clinical research.

334

335 **2. Recommendations for the inclusion and study of sex-specific to preclinical research**
336 **(PC)**

337 ***PC Recommendation 1: Researchers should be aware of, and report on, the sex of the established***
338 ***cell lines, primary cells and tissues used in their research***

339 Although the majority of respondents to the PAINDIFF survey indicate that they sometimes or always
340 consider the sex of organisms from which tissue samples arise, the majority rarely or never consider
341 the sex of cell lines they use in their research (Supplementary Table S2 Q19-22). This sex omission and
342 male bias in cell experiments is well recognised⁵⁰ despite the authentication of cell line sex being

343 recommended or mandated by many funding agencies. Researchers should use cells and tissues from
344 both sexes in their research and should consider assessing the impact of sex-linked genes on
345 phenotype and functional responses.

346

347 ***PC Recommendation 2: It is not always necessary to test for oestrous cycle stage***

348 Research exploring the impact of the oestrous cycle on sensory and affective pain responses, as well
349 as the effectiveness of analgesics, remains limited. Findings are often inconsistent, varying according
350 to the strain, experimental model, or mechanisms studied. Furthermore, some sex differences are
351 known to be due to testosterone (e.g.⁵¹) and not oestrogen and thus examination of effects across
352 oestrous cycle in such instances would not be relevant. Our survey data indicate that the majority of
353 preclinical pain researchers either never or rarely assess or consider oestrous cycle in their studies
354 citing various reasons (see Supplementary Table S2 Q30-33) with the most common themes being: (1)
355 *Oestrous cycle is not the focus of the research; (2) it has been already shown or expected that it has*
356 *no/little effect; (3) the effect of sex in a pain model should be there regardless of phases; (4) only*
357 *analyzed if observed variability in females is greater than males; (5) it increases stress of animals; (6)*
358 *concern of equivalent testing in males.* Decisions on whether to analyse for oestrous cycle should be
359 informed by existing evidence, and may be dependent on the pain model, test/assay, and question
360 under investigation. In cases where a lack of sex difference is observed in the primary outcome
361 measure, it should be acknowledged that sex differences may only become apparent when females
362 are in a particular stage of the oestrous cycle.

363 ***PC Recommendation 3: Researchers should include detailed reporting on housing, environmental***
364 ***conditions and experimental design***

365 Expanding on Universal Recommendation 4, specific details should be considered and reported in
366 preclinical research studies. Our survey data reveal a varied approach to housing, environmental
367 conditions and testing order among preclinical pain research respondents (see Supplementary Table
368 S2). The decision regarding these factors appears to be influenced by the experimental questions and
369 the available human and infrastructural resources available. However, it was noted that researchers
370 are more likely to behaviourally test each sex separately on different days or sequentially on the same
371 day with males most commonly tested first (see Supplementary Table S2 Q23). The most common
372 reason cited was the possible influence of pheromones and odours on experimental parameters
373 between the sexes tested at the same time. As such, detailed reporting should include information on
374 1) housing and environmental conditions (e.g., cage density, cage type, diet, age/weight of animal,
375 presence and type of environmental enrichment, light cycle and lux in testing and holding rooms,
376 humidity and temperature, if both sexes in same or different holding room/rack) and 2) experimental
377 design (inclusion of both sexes in the same or different cohort/batches, control for age/weight, order
378 and sequence of testing, time of day of testing/samples taken, randomisation and blinding).

379

380 **3. Recommendations for the inclusion and study of sex- and gender-specific to**
381 **human/clinical research (H/C)**

382 **H/C Recommendation 1: Ask for participants' sex assigned at birth and self-identified gender.**

383 There is a substantial body of research acknowledging that there are both conceptual and operational
384 differences between sex as a biological variable and gender as a socio-psychological variable. We
385 recommend that researchers ask participants to report both their sex assigned at birth and also their
386 gender identity as a way of acknowledging that these may not necessarily align. However, researchers

387 must also be acutely aware of barriers (including cultural, legal and religious) which may pose risks for
388 researchers and participants in asking and answering these questions, and omission of this
389 information should be justified.

390

391 **H/C Recommendation 2. Include a ‘prefer/choose not to say’ response option when asking about**
392 **sex and gender.**

393 For the reasons outlined in recommendation 1, it is preferable to include a ‘prefer/choose not to say’
394 response option when asking about sex and gender’, except for studies where information on the sex
395 and/or gender of each participant is essential to the aims of the study, or for health and safety reasons.
396 In such studies, it should be made clear in the participant information and informed consent
397 documents that participants will be required to declare their sex and/or gender, why this information
398 is necessary in the study, and that they can choose not to participate in the study if they prefer not to
399 declare their sex and/or gender.

400

401 **H/C recommendation 3. Include an open textbox response option to capture gender identity**
402 **followed by a series of tick boxes to aid categorisation.**

403 Although the importance of being able to categorize respondents is evident, it is the case that
404 concepts related to gender are changing rapidly and pre-existing categories may not capture some
405 nuances in gender identity. The provision of an open text option takes account of this⁵². Engagement
406 with lived experience consultants and community partners can provide a valuable resource for
407 ensuring the use of current, appropriate terminology. Researchers may also consider whether other
408 aspects of gender (e.g., gender expression, gender role orientation) may also be relevant to collect.

409

410 **H/C Recommendation 4. Report the number of people who hold diverse gender identities and,**
411 **where possible and permitted, make the raw data accessible for further study (while ensuring**
412 **anonymity).**

413 Increasing data suggests gender-diverse groups experience unique sources of pain (e.g., associated
414 with gender affirming practices) and that pain must be considered in the context of minority stressors
415 and sources of resilience^{34,53}. Although it may not be possible to conduct meaningful analysis of small
416 numbers within a given gender-identity group in any individual study, researchers should, when
417 possible and permitted, make their data available through a repository to facilitate data pooling across
418 the research community. This may ultimately lead to a better understanding of pain experience in
419 diverse groups. Researchers should consult available guidelines on the ethical conduct of research
420 with gender-diverse populations (e.g.⁵⁴). The decision on making such data widely accessible, together
421 with data management and storage, should comply with any relevant data protection/privacy
422 regulations in force within the relevant jurisdiction.

423

424 **H/C Recommendation 5. When possible, collect and report on sex-specific variables to allow**
425 **disaggregated analysis by sex or gender to be better informed by hormonal status, rather than solely**
426 **by age.**

427 Given the documented role of sex hormones in understanding sex/gender influences in pain, it is
428 important to collect data on sex-specific variables such as menstrual cycle phase, puberty, use of

429 contraceptives, menopause status, or other hormone modifying/replacement treatment. However, it
430 is acknowledged that there may be barriers (including cultural and religious, or questions of relevance)
431 that may make it difficult for researchers and participants to ask and answer these questions.

432

433 Table 1 provides a checklist of recommendations for researchers for the inclusion, study and
434 transparent reporting of sex and/or gender in preclinical and human/clinical research.

435

436 **Discussion and Conclusion**

437 This paper presents a set of recommendations on methodological approaches for best practice study
438 and reporting of sex and gender as variables in pain research, which are broadly applicable across the
439 spectrum of biopsychosocial research. Informed by the literature and the survey of pain researchers
440 on current practice and opinions, five universal recommendations that apply to both preclinical and
441 human/clinical research were identified, with additional recommendations pertaining specifically to
442 either preclinical or human/clinical research. Although the universal recommendations pertain to the
443 inclusion and study of sex in both preclinical and clinical research, these recommendations also apply
444 to the inclusion and study of gender in human/clinical research. There is increasing awareness of pain
445 inequities in gender-diverse groups, and the relevance of gender on pain for all people beyond the
446 impact of sex assigned at birth^{34,53,55}. We advocate for further scientific attention to the role of gender
447 and the integration of sex and gender research in pain, so that this field can move forward with respect
448 to rigorous methodology and clear conclusions. Although the recommendations were developed
449 through the lens of applicability to pain research, they align with those published for other
450 disciplines^{15-17,56} and the National Institutes of Health Four Cs of Studying Sex to Strengthen Science⁵⁷,
451 and thus are widely applicable across the biopsychosocial sciences.

452 We believe that widespread adoption and implementation of the proposed recommendations will
453 reduce variability, facilitate reproducibility between research settings, and improve the translatability
454 of research findings within and beyond the field of pain, leading to better outcomes for patients.
455 However, we also acknowledge limitations relating to the low number of respondents to the survey
456 from countries in Latin and South America and Africa, and that consensus was reached by open
457 discussion rather than the use of a structured process such as Delphi. In addition to these
458 recommendations, the results of the PAINDIFF survey (Supplementary Tables S2-4) provides a valuable
459 resource for researchers. For some methodological aspects it was not possible to recommend a single
460 standardised approach due to the wide variety of practices employed across and within research
461 settings, and the paucity of compelling evidence in favour of one approach over another. However,
462 the survey results we provide will enable readers to gain insight into various methodological
463 approaches that are used internationally, and the extent to which these are used or favoured by the
464 international pain research community. This will better equip readers to make informed decisions for
465 their research.

466 Our recommendations are of relevance to, and have implications for, multiple stakeholders, including
467 researchers (both within and outside of the pain field), funding agencies, journal editors,
468 governments, policymakers, patients and the public (Figure 5). Despite the challenges involved in
469 undertaking such research, there must be widespread recognition, acknowledgement, and
470 understanding by funding agencies, journal editors, journal and grant reviewers, regulatory
471 authorities, institutional ethics committees, facilities management (animal and clinical), and
472 researchers themselves, that greater resources are required to study sex and gender as variables in

473 pain research. This includes but is not limited to financial resources, infrastructural resources, time,
474 and human resources. It is also important to recognise and acknowledge that there will be some
475 research areas or questions where there is little or no rationale for the inclusion of multiple sexes or
476 genders. There will also be studies where a comprehensive, fully powered investigation of the
477 influence of sex or gender is not the primary aim of the study. However, males and females should be
478 included as standard unless there is a valid reason not to do so, and researchers are encouraged to
479 consider conducting secondary analysis to assess sex/gender as a variable and/or calculate the power
480 required to inform experimental design for future studies that might pursue evaluation of the
481 influence of sex/gender. Encouragingly, eight of the key pain journals (including *PAIN*, *The Journal of*
482 *Pain* and *European Journal of Pain*) have agreed to improve the practice of ensuring diverse
483 representation across scientific pain work^{1,4,58,59}.

484 In conclusion, the work described herein provides a novel, impactful, expert-led methodological
485 framework and recommendations for studying and reporting sex and gender as variables in preclinical,
486 clinical and translational pain research in a manner that should decrease variability of findings and
487 improve reproducibility between laboratories and research settings. Furthermore, much of the
488 content and recommendations have general relevance beyond pain research, to other areas of
489 biomedical and psychological research in which sex and gender are studied as variables.

490

491

492

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500 <https://BioRender.com/75gd0sg>; <https://BioRender.com/hac6a6y>].

501

502

503 **Figure Legends**

504 **Figure 1:** Demographics of the PAINDIFF Survey participants (n = 483). Data were collected on sex,
505 gender, primary place of work, country in which institution is situated, career stage, if principal
506 investigator, and primary research area. See Supplementary Table 1 for breakdown of demographics
507 for those that completed the preclinical, human/clinical or both arms of the survey.

508 **Figure 2:** Opinions and practice on the inclusion and study of sex and/or gender in preclinical and
509 human/clinical pain research. Data depicts % of responses for each question. See Supplementary
510 Table 2 for full data set.

511

512 **Figure 3:** The concerns and barriers that may prevent researchers from conducting sex and/or
513 gender studies and analysis (Q94) presented for (a) all respondents and those that completed the (b)
514 preclinical and (c) human/clinical surveys.

515 **Qualitative Survey: The most common themes for researchers not always carrying out pain-related**
516 **research in more than one sex or gender differ for preclinical and human/clinical research**

517 Most common themes for not using both sexes in **preclinical research**

- 518 • *Lack of time, money, personnel, space for animal housing, or other resources*
- 519 • *The condition or the effect of interest is present in only one sex*
- 520 • *Proof of concept or Pilot-experiments*
- 521 • *Previous work showing no sex differences*
- 522 • *Females are easier/more difficult to handle*

523

524 Most common themes for not using more than one sex in **human/clinical research**

- 525 • *The condition is much more prevalent in one sex*
- 526 • *Sex differences are not the focus of the research*
- 527 • *Lack of funding, time or participants availability to allow for an adequate sample size*
- 528 • *Intersex sample size is too small*

529

530 Most common themes for not examining gender in **human/clinical research**

- 531 • *The condition is much more prevalent in one gender or gender is not the focus of the*
532 *research*
- 533 • *Lack of clear definitions/standards/guidelines on distinction between sex and gender*
- 534 • *Sample size too small for categories other than men and women*
- 535 • *Patients not understanding the difference between sex/gender or reluctant to declare their*
536 *gender*
- 537 • *Not, or not easily, permitted from the state/institution/culture*

538

539 **Figure 4:** PAINDIFF recommendations for the inclusion and study of sex and gender in research.

540 **Figure 5:** Recommendations for key stakeholders including researchers, journal editors and
541 reviewers, funders, policy makers, societies, public bodies and patients to ensure that the
542 importance of including and studying sex and gender in research is acknowledged, funded and
543 supported.

544

545 **Table 1: Checklist of recommendations for the inclusion and study of sex and gender in preclinical**
 546 **(PC) and human/clinical (H/C) research**

#	Recommendation	Preclinical	Human/Clinical
Universal			
1	Males and females included		
2	Sex accounted for in randomization/ counterbalancing/ testing order		
3	Study powered for sex differences (not always necessary)		
4	Detailed reporting of experimental design, including sex of experimenter (when possible) included		
5a	Sex-disaggregated analysis conducted		
5b	Sex-disaggregated data reported		
PC1	Sex of the cells and/or tissues identified		
PC2	Oestrous cycle stage accounted for (not always necessary)		
PC3	Detailed reporting on housing and environmental conditions included		
H/C1a	Participant's sex assigned at birth included in demographics		
H/C1b	Participant's self-identified gender included in demographics		
H/C2	"Prefer/choose not to say" response option included		
H/C3	Textbox response option to capture subjective individual identity included in demographics		
H/C4	Number of people who are gender diverse reported		
H/C5	Sex and gender specific variables collected and reported		

547

548

549

550

551 **Box 1: Definitions and Terminology related to Sex and Gender**

552 The definitions and terminology related to Sex and Gender used in this manuscript are derived from
553 multiple resources (see ⁶⁰⁻⁶²).

554 **Sex** is a biological construct that refers to the reproductive anatomy, chromosomes and physiology,
555 genetics, and hormonal levels and function associated with being genetically or phenotypically male
556 or female. This term is used for both human and non-human animals and is generally referred to as a
557 male-female binary, though there can be significant variation in the anatomical and physiological
558 presentation within each sex category. Genotypic sex refers to the sex chromosomes (i.e., XX, XY, or
559 another variation) that influence sex development, whereas phenotypic sex is the expression of sex
560 through reproductive organs, genitalia, and secondary sex characteristics. In humans, **sex assigned at**
561 **birth** refers to the designation of sex at birth, generally determined on inspection of visible genitalia.
562 **Intersex** (also referred to as **differences of sex development** or **variations of sex traits**) refers to
563 humans who are born with sex characteristics that are outside of what is generally assigned as male
564 or female anatomy. This may be related to genetic variations but can also be influenced by hormonal
565 or other factors. Non-human animals that produce both male and female gametes are referred to as
566 **hermaphrodites**.

567 **Gender** is a psychosocial construct that refers to characteristics, attitudes, attributes, behaviours,
568 identities, norms, and expectations that are associated with certain sex traits. This commonly includes
569 **gender identity**, which is a person's felt sense of their own internal gender (or lack thereof), which
570 may or may not align with their sex assigned at birth. If an individual's gender identity matches their
571 sex assigned at birth, they may be referred to as **cisgender**, and if their gender identity does not match
572 their sex assigned at birth, they are referred to as **transgender** or **gender-diverse** (note: many
573 individuals, including those with non-binary gender identity, may have a gender that does not match
574 their sex assigned at birth but not identify with the term transgender). **Gender expression** is how an
575 individual shares or communicates their gender to others through behaviours, mannerisms,
576 appearance, clothing, social roles, etc., which may or may not align with their gender identity. **Gender**
577 **roles, norms and relations** refer to the societal and cultural expectations of how an individual should
578 act on account of their gender and can be described in relation to levels of power and privilege
579 conferred on the basis of gender. While often described in relation to a woman-man binary, gender is
580 increasingly recognized as encompassing a broad spectrum of identities and expressions.

581

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719 **Supplementary Data**

720 Supplementary Table S1: Demographic data on PAINDIFF Survey Respondents

721 Supplementary Table S2: Quantitative data from PAINDIFF Survey

722 Supplementary Table S3: Quantitative data from PAINDIFF Survey presented by sex

723 Supplementary Table S4: Quantitative data from PAINDIFF Survey presented by gender

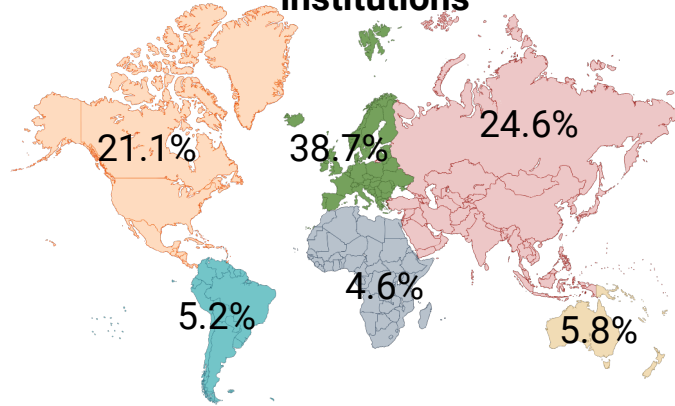
724 Supplementary Data 1: PAINDIFF Survey Questions as presented in Qualtrics

725

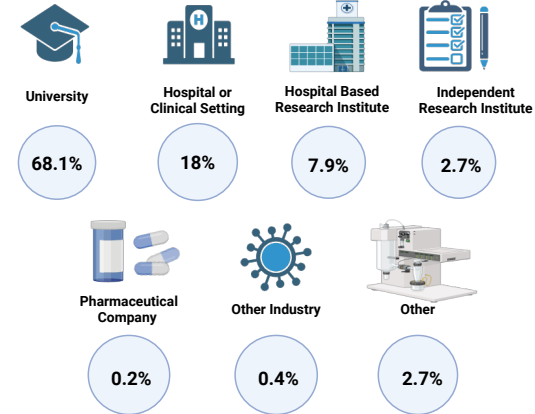
Demographics of the PAINDIFF Survey Participants

Survey Respondents	Number
Total	483
Preclinical	160
Human/Clinical	293
Both Survey Arms	30

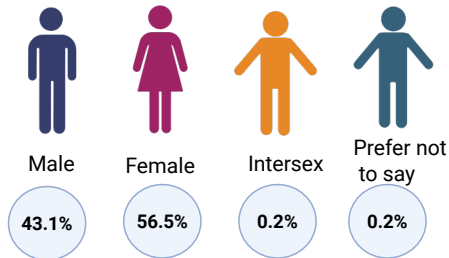
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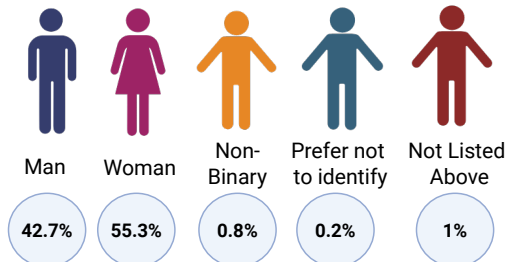
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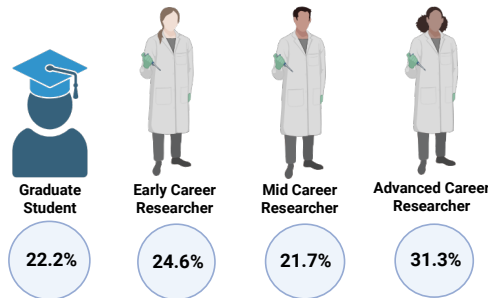
Sex



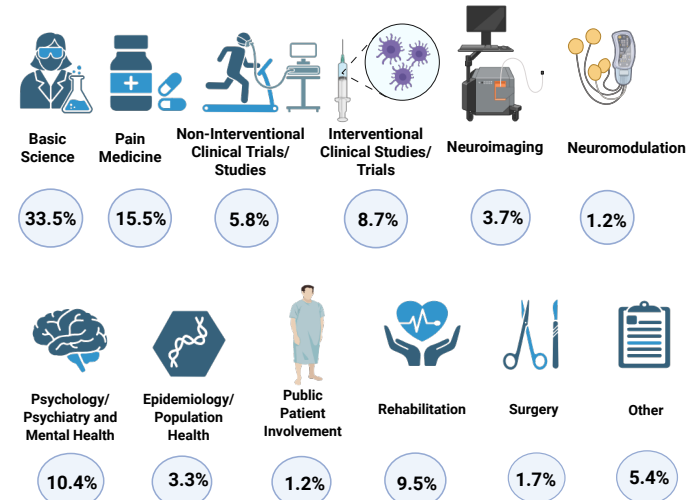
Gender



Career Stage



Primary Research Area

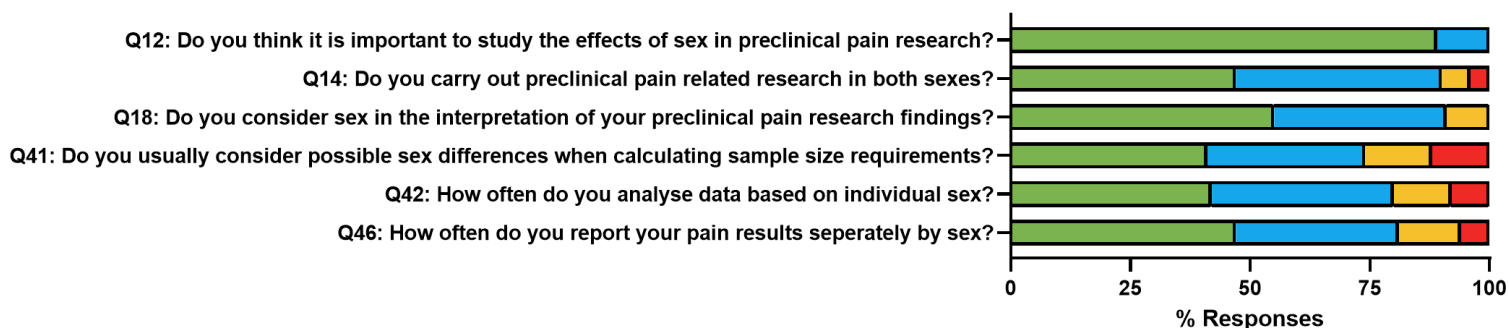


Are you a Principal Investigator leading your own research team?

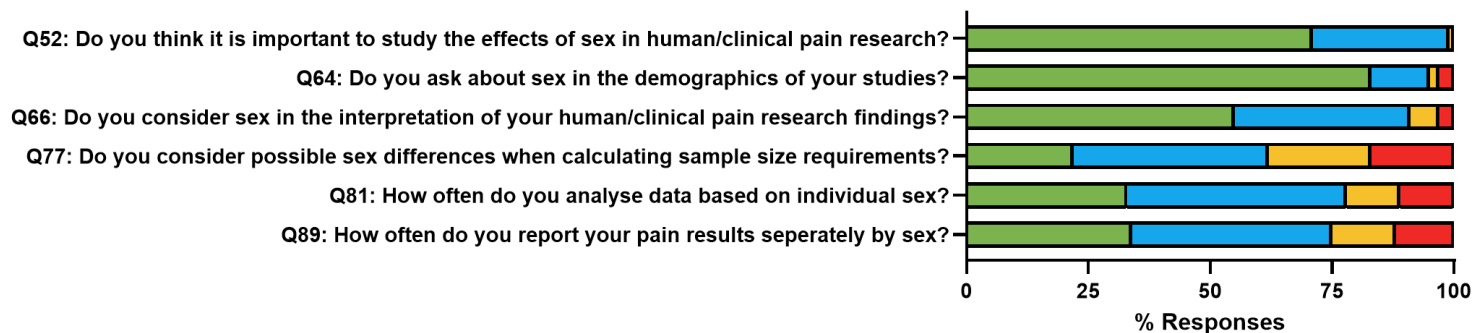


■ Always
 ■ Sometimes
 ■ Rarely
 ■ Never

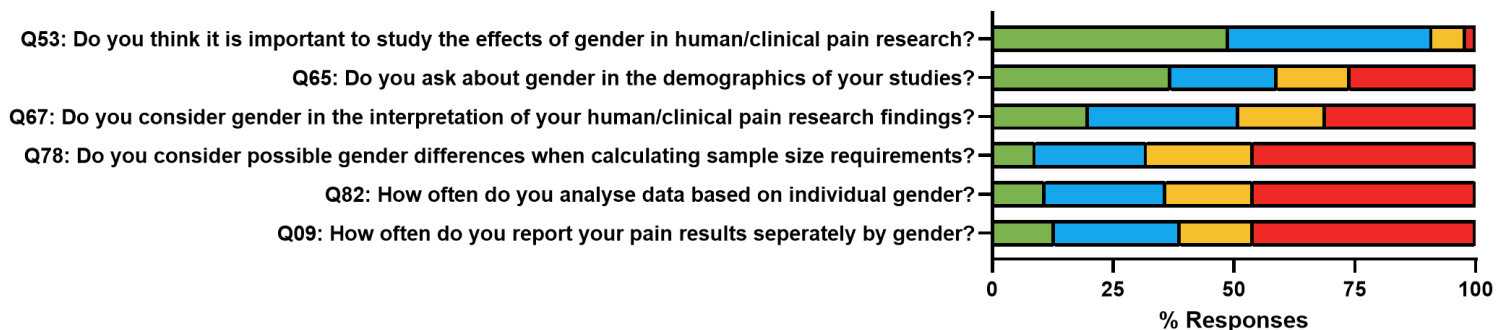
Preclinical



Human/Clinical (Sex)



Human/Clinical (Gender)



(a) What are the concerns and barriers that may prevent you from conducting sex and/or gender studies and analyses



- 25.33% Lack of information, knowledge, expertise
- 20.47% Financial resources
- 16.05% Time
- 12.22% Human resources
- 11.19% Sex and/or gender differences are not relevant to my research question
- 5.45% Other
- 9.28% No barriers

No. of Repondents = 322

(b) Preclinical



- 11.07%
- 28.69%
- 23.36%
- 13.52%
- 11.07%
- 2.05%
- 10.25%

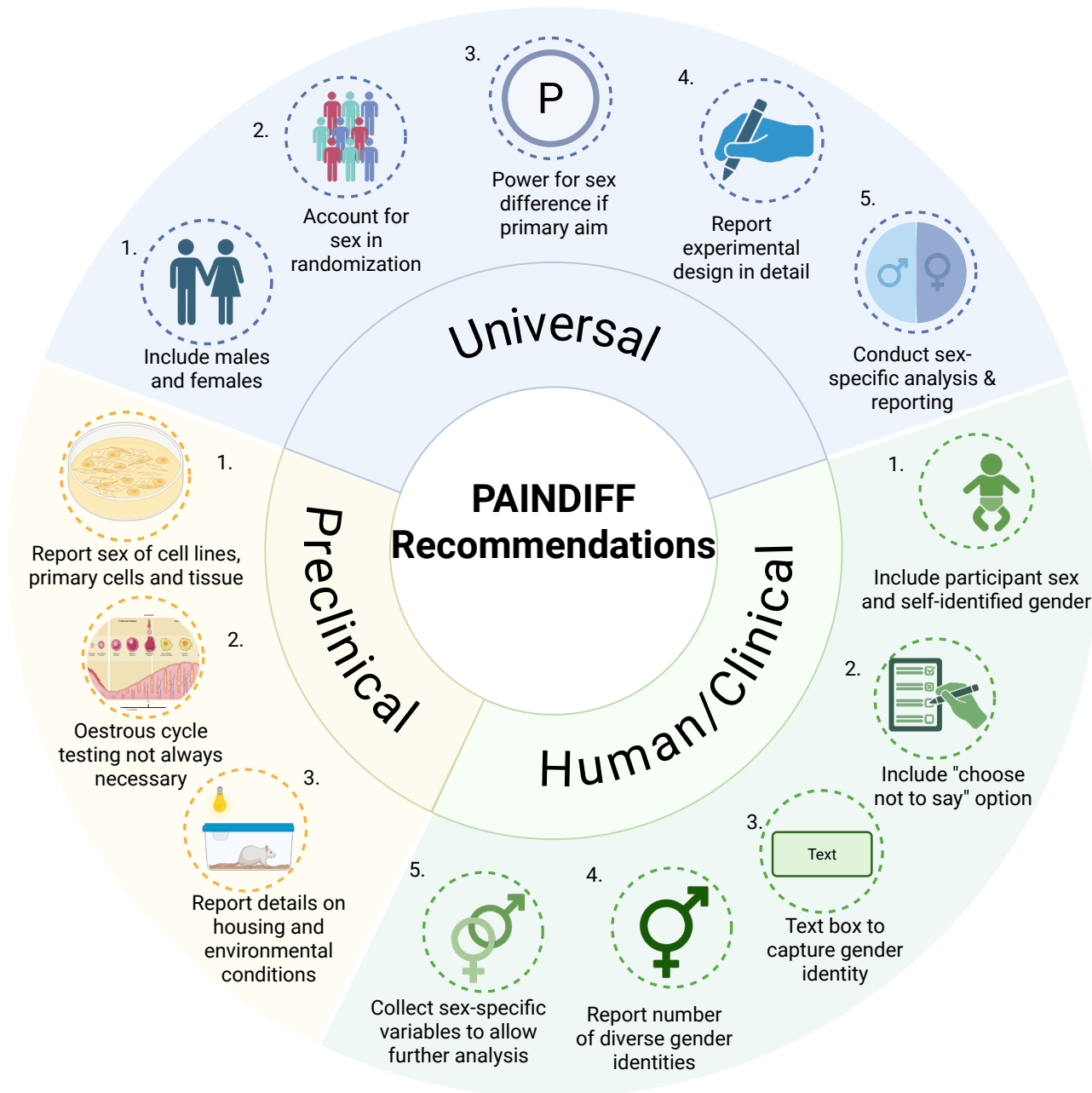
No. of Repondents = 118

(c) Human/Clinical



- 33.69%
- 14.85%
- 11.94%
- 11.41%
- 11.14%
- 7.69%
- 9.28%

No. of Repondents = 178



Stakeholder Recommendations

- Consider sex and/or gender in research hypothesis, aim & design
- Report detail on study design and methodology
- Report data (and analyse if possible) in sex/gender-disaggregated manner
- Discuss implications of sex and gender effects

- Adopt sex and gender equality in research guidelines
- Ensure all sexes/genders included or adequate justification provided
- Ensure data reported (and possibly analysed) in sex/gender disaggregated manner
- Ensure sex/gender implications considered and discussed

- Incorporate sex and gender inclusion policy
- Acknowledge sex and gender research requires additional resources
- Allocate additional funding to sex and gender in research

- Policy to be informed by sex and gender research
- Societies to advocate for sex and gender research and funding
- Ensure public and patient involvement in research
- Deliver research-informed care for all