A. Appendix: Systematic Reviews on the Impact of Consent on Health Research

In this appendix we present the results from two systematic reviews of the literature to identify the impact of consent on the process and outcomes of health research. The first review focused on systematic reviews already conducted in the context of recruiting participants in clinical trials. Therefore, it was effectively a review of systematic reviews. The reason we reviewed systematic reviews was because this question, in the context of clinical trials, had already been studied extensively and there were already a number of systematic reviews that were done. The second systematic review focused on original research investigating the impact of consent models on observational studies, including studies that use pre-existing databases.

A.1 Review 1: Systematic Review of Consenter Differences in Clinical Trials

We wanted to identify and summarize studies examining differences between those who consent to participate in clinical trials and those who do not. Because of the large number of articles that investigate this issue, we limited our research to meta-analyses and systematic reviews that have already been conducted.

A.1.1 Search methods

The search strategy was developed by an information specialist, in consultation with the primary author. A PubMed Related Articles search was first conducted from initial seed articles. A broad search of MEDLINE was then conducted for systematic reviews related to reasons or factors affecting potential research subjects' willingness to give consent for research participation or affecting study withdrawal or opt-out. Both subject headings and free-text terms were used, and searches were limited to publications in English.

MEDLINE Search Strategy (Ovid; 1950 to June Week 2 2007)

1. Attitude/ or Communication barriers/ or Comprehension/

2. Decision Making/ or Disclosure/

3. Motivation/ or Patient Participation/ or Patient Selection/

4. Refusal to Participate/ or Research Subjects/ or Researcher-Subject Relations/

5. Physician-Patient Relations/ or Professional-Patient Relations/

6. exp informed consent/ or Confidentiality/

7. (Opt-in or opt in or opt-out or opt out or non-consent or no consent or full consent or explicit consent).tw.

8. ((waive$ adj3 consent) or waiver or consent status or (consent adj3 model)).tw.

9. Selection bias/

10. ((Predictor$ or express$ or knowledgeable) adj3 consent).tw.

11. ((decline$ adj3 entry) or nonentry or non-entry).tw.

12. ((decline$ or willing$ or refus$) adj3 (participat$ or enroll$ recruit$)).tw.

13. authorization bias.tw.

14. ((consent or response or recruitment or participation or refusal or accrual) adj3 (strateg$ or method$ or technique$ or approach$ or reason$ or factor$ or incentive$ or disincentive$ or motivat$ or barrier$ or attitude$ or intervention$ or effective$ or increas$)).tw.

15. (research or study or studies or trial$ or survey$ or questionnaire$ or audit or audits or registry or registries).tw.

16. or/1-14

17. and/15-16

18. limit 17 to (case reports or comment or letter or newspaper article)

19. 17 not 18

20. limit 19 to meta analysis

21. limit 19 to "topic reviews (cochrane)"

22. ((systematic$ adj3 review$) or meta analy$ or meta-analy$).tw.

23. evidence report technology assessment summary.jn.

24. (health technology assessment reports or health technology assessment rockville md or health technology assessment winchester england).jn.

25. or/22-24

26. and/19,25

27. or/20-21,26

28. limit 27 to english language

A.2 Results

A total of 34 articles were retrieved for level 1 screening. Articles were excluded at level one if they did not focus on factors that influence consent in clinical trials. Seven articles were excluded at this level, leaving 27 articles at level 2. Articles were excluded at level 2 if they were in a format other than a systematic review or meta-analysis. Five articles were excluded at this level. The final number included and data extracted was 22.

Out of the remaining 22 articles, 2 were promoted to the second systematic review due to their focus on observational health research, rather than clinical trials. Fifteen articles that provided information pertinent to patient characteristics were summarized. The other five articles were excluded from the summary as they focused on physician factors and/or study design characteristics and their impact on consent and recruitment.

A summary of the findings is provided in Table 1.

Bias Factors due to Consent	Explanations
Age [1-7]	- youth consent is hindered by parental consent requirements - the findings for adults are contradictory: in some studies older adults are found to be more likely to consent and in other cases younger adults are found to be more likely to consent - one review looking exclusively at participation in the elderly (65+) found that the elderly are less likely to consent and/or be asked to participate in clinical trials [1]
Sex [2, 4-8]	- women of childbearing age are historically excluded from clinical trials - males are generally found to be more likely to participate
Socio-economic background/status [2, 4, 6, 9]	- studies are contradictory, showing high consent levels for those of low SES in some studies [2], but low rates for those with low SES who are also a part of a minority group (i.e., ethnic minorities [6, 9] and women) - in cancer trials, consent rates were found to be low for those with lower SES [4]
Ethnicity/race [3, 4, 6, 8-13]	- those from the ethnic majority are more likely to consent/participate then those of an ethnic minority - ethnic minorities may be offered fewer opportunities to participate [6]
Location [4, 6]	- those in rural locations/communities were found to be less likely to participate as opposed to those in urban areas
Education [2, 5]	- a lower level of education was shown generally to increase consent vs. a higher level of education
Language [6]	- those who speak the predominant language are more likely to consent and/or be asked to participate in trials vs. those who do not speak the language
Religiosity [6, 10]	- one review found that religiosity decreased consent in some studies and increased consent in others [10] - on the other hand, another review found no literature on religious barriers in trials, indicating that there has not been much research conducted in this area [6]
Health [1, 3, 4, 7, 9, 13-15]	- generally, the research shows that low/no co-morbidity increases the likelihood of participation - as the stages of one's disease progress (early – late), consent becomes less likely - one article presents contradictory evidence: that later stage disease/more co-morbidity increases participation [7] - in prevention trials, those with a healthy lifestyle are more likely to participate [7]
Social support [7, 14]	- inadequate social support indicates greater consent in some studies [7] but lower consent in others [14]

Table 1: Summary of patient characteristics that differ between consenters and non-consenters in clinical trials.

A.3 Review 2: Impact of Consent Models on Observational Health Research

In our second review, we focused on original research studies that examined the impact of different consent models on observational health research. An American Medical Informatics Association panel defined explicit consent to include opt-in and opt-out methods of seeking consent. Implied consent was defined as no consent for participation with or without notice to subjects [16]. For implied consent, we assume a participation rate of 100% as all eligible subjects would by definition be included.

For those studies focusing on opt-in consent, we considered only active consent (as opposed to passive consent) where the participants have to actively agree to participate or to continue to participate in the study. Opt-in passive consent is used in studies like surveys in which consent is not openly requested but a reply is considered to entail one's consent to participate. With active consent the subjects maintain control over whether or not they participate, as opposed to with implied consent where no declaration of consent is sought and therefore no informative data can be produced on the effect of consent on the outcomes of such studies.

Consequently, we excluded opt-in studies using passive consent, such as those looking only at response rates to questionnaires and those employing proxy consent in which someone other than the subject provided consent. However, survey-based studies were included where consent was requested for participation in the survey itself or to linkage with or review of respondents' medical record data. For example, a study by Beebe and colleagues looking at the effect of consent on survey response rate compared the response rate from a group receiving a HIPAA authorization form & survey questionnaire, to the response rate from those sent the questionnaire only [17].

A.3.1 Search Strategy

Databases were selected on the basis of subject coverage. The search strategy was developed by an information specialist, in consultation with the primary author. The following databases were searched: MEDLINE (Ovid; 1950 to July Week 1 2007), CINAHL (Ovid; 1982 to July Week 1 2007), PsycINFO (Ovid; 1806 to August Week 2 2007), The Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid; 3rd Quarter 2007), The Cochrane Methodology Register (CMR) (The Cochrane Library; Issue 3, 2007), PAIS International (CSA; 1972 to August 2007), and the Social Sciences Citation Index (ISI Web of Science; 1981 to August 25, 2007). We searched for records related to a combination of the following 3 concepts, customized for each database: consent models/privacy considerations, bias/other outcomes, and observational health research. Both subject headings and free-text terms were used.

Searches were limited to publications in English and to the publication dates 1990-2007 since privacy legislation directly relevant for observational health research was first introduced in the 1990s (i.e., HIPAA).

Additional articles were obtained through reviewer nomination and by checking the Annotated Bibliography (2007) prepared for the meetings of the U.S. Institute of Medicine's *Committee on Health Research and the Privacy of Health Information: The HIPAA Rule* [18].

A.3.1.1 Medline Search Strategy

1. exp informed consent/
2. privacy/
3. HIPAA.mp.
4. "Health Insurance Portability and Accountability Act"/
5. Confidentiality/
6. (Opt-in or opt in or opt-out or opt out or non-consent or no consent or full consent or explicit consent).tw.
7. (waive$ adj3 consent).tw.
8. (waiver or consent status).tw.
9. (consent adj3 model$).tw.
10. (identifiable adj3 (data or information)).tw.
11. Data Protection Act.tw.
12. (Health and Social Care Act).tw.
13. Human Rights Act.tw.
14. (Caldicott or PIPEDA or Personal Data Protection Directive).tw.
15. privacy adj3 act$).tw.
16. De-identif$.tw.
17. (Personal information protection and electronic documents act).tw.
18. (double-cod$ or double cod$ or single-cod$ or single cod$ or Re-identif$ or reidentif$ or deidentif$ or anonymiz$ or anonymis$ or pseudonymiz$ or pseudonymis$ or reconsent$ or anonymity or identifiability).tw.
19. ((express$ or knowledgeable) adj3 consent).tw.
20. (data adj3 unlink$).tw.
21. (strip$ or remov$ or delet$) adj3 identifier$).tw.
22. ((linked or linkable or coded) adj3 (information or data)).tw.
23. ((unidentif$ or non-identif$ or nonidentif$) adj3 (data or information)).tw.
24. or/1-23
25. Selection bias/
26. "bias (epidemiology)"/
27. patient selection/
28. sample size/
29. "costs and cost analysis"/ or cost-benefit analysis/

30. Time Factors/
31. ((consent or response or recruitment or participation or refusal$) adj3 rate$).tw.
32. (bias or biases).mp.
33. (survey$ adj3 (response$ or participation)).tw.
34. (Predictor$ adj3 consent).tw.
35. accrual.tw.
36. or/25-35
37. epidemiologic methods/ or data collection/ or exp health surveys/ or health care surveys/ or exp nutrition assessment/ or exp medical records/ or exp registries/ or epidemiologic studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/ or feasibility studies/
38. databases/ or exp databases, factual/
39. "quality of health care"/ or exp medical audit/ or nursing audit/ or program evaluation/ or exp health services research/
40. exp "outcome and process assessment (health care)"/ or quality assurance, health care/
41. (audit$ or registr$ or observational or epidemiolog$).tw.
42. ((health service$ or medical record$) adj3 (research or study or studies)).tw.
43. or/37-42
44. and/24,36,43
45. limit 44 to english language
46. limit 45 to yr="1990 - 2007"

A.3.1.2 CINAHL

1. Consent/ or "consent (research)"/
2. "confidentiality (research)"/ or "Privacy and Confidentiality"/
3. HIPAA.mp.
4. "Health Insurance Portability and Accountability Act"/
5. (Opt-in or opt in or opt-out or opt out or non-consent or no consent or full consent or explicit consent).tw.
6. (waive$ adj3 consent).tw.
7. (waiver or consent status).tw.
8. (consent adj3 model$).tw.
9. (identifiable adj3 (data or information)).tw.
10. Data Protection Act.tw.
11. (Health and Social Care Act).tw.
12. Human Rights Act.tw.
13. (Caldicott or PIPEDA or Personal Data Protection Directive).tw.
14. (privacy adj3 act$).tw.
15. De-identif$.tw.
16. (Personal information protection and electronic documents act).tw.
17. (double-cod$ or double cod$ or single-cod$ or single cod$ or Re-identif$ or reidentif$ or deidentif$ or anonymiz$ or anonymis$ or pseudonymiz$ or pseudonymis$ or reconsent$ or anonymity or identifiability).tw.
18. ((express$ or knowledgeable) adj3 consent).tw.
19. (data adj3 unlink$).tw.
20. ((strip$ or remov$ or delet$) adj3 identifier$).tw.
21. ((linked or linkable or coded) adj3 (information or data)).tw.
22. ((unidentif$ or non-identif$ or nonidentif$) adj3 (data or information)).tw.
23. or/1-22
24. "bias (research)"/ or nonresponse bias/ or sampling bias/ or selection bias/ or research subject recruitment/
25. patient selection/
26. sample size/
27. "costs and cost analysis"/ or cost-benefit analysis/
28. Time Factors/
29. ((consent or response or recruitment or participation or refusal$) adj3 rate$).tw.
30. (bias or biases).mp.
31. (survey$ adj3 (response$ or participation)).tw.
32. (Predictor$ adj3 consent).tw.

33. accrual.tw.
34. or/24-33
35. (audit$ or registr$ or observational or epidemiolog$).tw.
36. ((health service$ or medical record$) adj3 (research or study or studies)).tw.
37. research ethics/ or research methodology/ or data collection/ or data collection methods/ or data collection, computer assisted/ or data mining/ or exp observational methods/ or "record review"/
38. "quality of health care"/ or "outcomes (health care)"/ or outcome assessment/ or quality assessment/ or nursing audit/ or "process assessment (health care)"/ or program evaluation/
39. nutrition assessment/ or exp Medical Records/ or sampling methods/
40. CROSS SECTIONAL STUDIES/ or PROSPECTIVE STUDIES/
41. epidemiological research/ or exp health services research/
42. registries, disease/ or registries, implant/ or registries, organ/ or registries, trauma/ or surveys/ or exp vital statistics/
43. "QUALITY OF CARE RESEARCH"/ or Quality Assurance/ or Audit/ or databases/
44. or/35-43
45. and/23,34,44
46. limit 45 to english
47. limit 46 to yr="1990 - 2007"

A.3.1.3 PsycINFO

1. informed consent/
2. privacy/
3. HIPAA.mp.
4. “Health Insurance Portability and Accountability Act"/
5. Confidentiality/
6. (Opt-in or opt in or opt-out or opt out or non-consent or no consent or full consent or explicit consent).tw.
7. (waive$ adj3 consent).tw.
8. (waiver or consent status).tw.
9. (consent adj3 model$).tw.
10. (identifiable adj3 (data or information)).tw.
11. Data Protection Act.tw.
12. (Health and Social Care Act).tw.
13. Human Rights Act.tw.
14. (Caldicott or PIPEDA or Personal Data Protection Directive).tw.
15. (privacy adj3 act$).tw.
16. De-identif$.tw.
17. (Personal information protection and electronic documents act).tw.
18. (double-cod$ or double cod$ or single-cod$ or single cod$ or Re-identif$ or reidentif$ or deidentif$ or anonymiz$ or anonymis$ or pseudonymiz$ or pseudonymis$ or reconsent$ or anonymity or identifiability).tw.
19. ((express$ or knowledgeable) adj3 consent).tw.
20. (data adj3 unlink$).tw.
21. ((strip$ or remov$ or delet$) adj3 identifier$).tw.
22. ((linked or linkable or coded) adj3 (information or data)).tw.
23. ((unidentif$ or non-identif$ or nonidentif$) adj3 (data or information)).tw.
24. or/1-23
25. Selection bias/
26. "bias (epidemiology)"/
27. client characteristics/ or client participation/ or patient selection/
28. sample size/
29. "costs and cost analysis"/
30. Time/
31. ((consent or response or recruitment or participation or refusal$) adj3 rate$).tw.
32. (bias or biases).mp.
33. (survey$ adj3 (response$ or participation)).tw.
34. (Predictor$ adj3 consent).tw.
35. accrual.tw.
36. or/25-35

37. exp experimentation/ or experimental attrition/ or exp experimental design/ or experimental subjects/ or exp methodology/ or exp "sampling (experimental)"/ or exp medical records/ or data collection/ or epidemiology/ or exp surveys/ or needs assessment/ or exp questionnaires/ or exp experimental methods/ or exp "quality of services"/
38. databases/
39. clinical audits/ or program evaluation/
40. quality control/
41. (audit$ or registr$ or observational or epidemiolog$).tw.
42. ((health service$ or medical record$) adj3 (research or study or studies)).tw.
43. or/37-42
44. and/24,36,43
45. limit 44 to english language
46. limit 45 to yr="1990 - 2007"

A.3.1.4 CENTRAL

1. exp informed consent/
2. consent.kw.
3. privacy/
4. privacy.kw.
5. HIPAA.mp.
6. "Health Insurance Portability and Accountability Act"/
7. "Health Insurance Portability and Accountability Act".kw.
8. Confidentiality/
9. Confidentiality.kw.
10. (Opt-in or opt in or opt-out or opt out or non-consent or no consent or full consent or explicit consent).tw.
11. (waive$ adj3 consent).tw.
12. (waiver or consent status).tw.
13. (consent adj3 model$).tw.
14. (identifiable adj3 (data or information)).tw.
15. Data Protection Act.tw.
16. (Health and Social Care Act).tw.
17. Human Rights Act.tw.
18. (Caldicott or PIPEDA or Personal Data Protection Directive).tw.
19. (privacy adj3 act$).tw.
20. De-identif$.tw.
21. (Personal information protection and electronic documents act).tw.
22. (double-cod$ or double cod$ or single-cod$ or single cod$ or Re-identif$ or reidentif$ or deidentif$ or anonymiz$ or anonymis$ or pseudonymiz$ or pseudonymis$ or reconsent$ or anonymity or identifiability).tw.
23. ((express$ or knowledgeable) adj3 consent).tw.
24. (data adj3 unlink$).tw.
25. ((strip$ or remov$ or delet$) adj3 identifier$).tw.
26. ((linked or linkable or coded) adj3 (information or data)).tw.
27. ((unidentif$ or non-identif$ or nonidentif$) adj3 (data or information)).tw.
28. or/1-27
29. Selection bias/
30. "bias (epidemiology)"/
31. patient selection/
32. patient selection.kw.
33. sample size/
34. (sample size or sampling).kw.
35. "costs and cost analysis"/ or cost-benefit analysis/
36. (cost-benefit analysis or cost or COST EFFECTIVENESS ANALYSIS).kw.
37. Time Factors/
38. time.kw.
39. ((consent or response or recruitment or participation or refusal$) adj3 rate$).tw.
40. (bias or biases).mp.
41. (survey$ adj3 (response$ or participation)).tw.

42. (Predictor$ adj3 consent).tw.
43. accrual.tw.
44. or/29-43
45. and/28,44
46. limit 45 to yr="1990 - 2007"

A.3.1.5 CMR

#1 (consent):ti,ab,kw or (privacy):ti,ab,kw or (confidentiality):ti,ab,kw or (HIPAA):ti,ab,kw or (identifiable data):ti,ab,kw, from 1990 to 2007 in Methods Studies

#2 (data):ti,ab,kw or (information):ti,ab,kw, from 1990 to 2007 in Methods Studies

#3 (non-identif*):ti,ab,kw or (nonidentif*):ti,ab,kw, from 1990 to 2007 in Methods Studies

#4 (waiver):ti,ab,kw or (identifier*):ti,ab,kw or (de-identif*):ti,ab,kw or (double-cod*):ti,ab,kw or (single-cod*):ti,ab,kw, from 1990 to 2007 in Methods Studies

#5 (Re-identif*) or (reidentif*) or (deidentif*) or (anonymiz*) or (anonymis*), from 1990 to 2007 in Methods Studies

#6 (pseudonymiz*):ti,ab,kw or (pseudonymis*):ti,ab,kw or (reconsent*):ti,ab,kw or (anonymity):ti,ab,kw or (identifiability):ti,ab,kw, from 1990 to 2007 in Methods Studies

#7 (identifiable):ti,ab,kw or (unlink*):ti,ab,kw or (link*):ti,ab,kw or (coded):ti,ab,kw or (unidentif*):ti,ab,kw, from 1990 to 2007 in Methods Studies

#8 (#3 OR #7), from 1990 to 2007

#9 (#2 AND #8), from 1990 to 2007

#10 (#1 OR #4 OR #5 OR #6 OR #9), from 1990 to 2007 in Methods Studies

A.3.1.6 PAIS

((consent or privacy or confidentiality or waiver or HIPAA or identifier* or de-identif* or double-cod* or single-cod* or re-identif* or reidentif* or deidentif* or anonymiz* or anonymis* or pseudonymiz* or pseudonymis* or reconsent* or anonymity or identifiability) and (research or study or studies or trial* or audit* or registry or registries or survey* or questionnaire* or observational or epidemiolog* or database*)) or (((data or information) within 3 (identifiable or unlink* or non-identif* or nonidentif* or link* or coded)) and (research or study or studies or trial* or audit* or registry or registries or survey* or questionnaire* or observational or epidemiolog* or database*))
Date Range: 1990 to 2007

Limited to: Published Works Only; Journal Articles Only; English Only

A.3.1.7 Social Sciences Citation Index

#8 #7 AND #6 AND #5 AND #2

DocType=Article OR Abstract of Published Item OR Letter OR Meeting Abstract OR Meeting Summary OR Meeting-Abstract OR Review; Language=English; Database=SSCI; Timespan=1990-2007

#7 TS=(research OR study OR studies OR trial* OR audit* OR registry OR registries OR survey* OR questionnaire* OR epidemiolog* OR database*)

#6 TS=(bias* OR "sample size" OR cost* OR accrual OR "consent rate" OR "response rate" OR "recruitment rate" OR "participation rate" OR "refusal rate" OR "survey response" OR "survey participation")

#5 #4 OR #3 OR #1

#4 TS=("de-identified data" OR "re-identified data" OR "reidentified data" OR "deidentified data" OR "anonymized data" OR "anonymised data" OR "de-identified information" OR "re-identified

information" OR "reidentified information" OR "deidentified information" OR "anonymized information" OR "anonymised data" OR pseudonymiz* OR pseudonymis* OR reconsent* OR identifier*)

#3 TS=("identifiable data" OR "unlinked data" OR "non-identifiable data" OR "nonidentifiable data" OR "linked data" OR "coded data" OR "identifiable information" OR "unlinked information" OR "non-identifiable information" OR "nonidentifiable information" OR "linked information" OR "coded information")

#2 TS=(medic* OR health* OR clinic* OR patient*)

#1TS=(consent OR privacy OR confidentiality OR HIPAA)

A.3.2 Results

The different consent models that were studied were: explicit consent, which included opt-in and opt-out consent; and implied consent, which included no consent/waiver of consent. Studies that only compared consenters to non-consenters were effectively comparing explicit consent to implied consent because under the latter approach all subjects would participate by default. We examined impacts on four dimensions: (a) recruitment rates, (b) selection bias, (c) the cost of doing observational health research, and (d) the time it takes to do observational health research.

Observational research spans a diverse set of activities, and consent can be sought at various points. Figure 1 illustrates a basic collection and disclosure workflow.

Some studies seek consent at the point of data collection from the patient and it is for using the data for a specific purpose. For example, Hollander et al, collected primary source data by way of patients interviews in their emergency room based survey on domestic abuse [19]. Consent was requested from patients prior to their participation in the interview.

Other studies seek consent at the point of data collection for the primary analysis and also for linkage to medical records or for subsequent specific or general disclosures of the original data for secondary purposes. For example, Young et al, involve both primary data collection from patients, and the use of data from existing databases which is typically linked to the primary source data. In Young's study, patients were sent a survey questionnaire which included a request for consent to data linkage [21]. Survey answers were then linked to medical record data if consent was provided. Tu et al, provide a good example of multiple consent requirements in their study of the Canadian Stroke Network Registry [22]. The researchers requested consent from eligible patients to be included in the registry, which would appear on the surface to be consent for primary data collection; however, the consent forms included a request for consent to both primary data collection and use of existing medical chart data, along with linkage to existing administrative databases, as well as the aggregation and release of data to external organizations [22].

Requesting consent at the point when data will be disclosed for secondary purposes is another approach. For example, Yawn et al, in which patients visiting an outpatient clinic were asked for consent to the use of their existing medical record data for research purposes [20].

Whether consent is sought for a primary analysis, data linkage, possible future disclosure, or disclosure of pre-existing records, and whether it is sought at the time of collection or disclosure, will likely have an impact on our main outcomes. However, it was not possible to differentiate these effects from the articles. Therefore we report overall results.

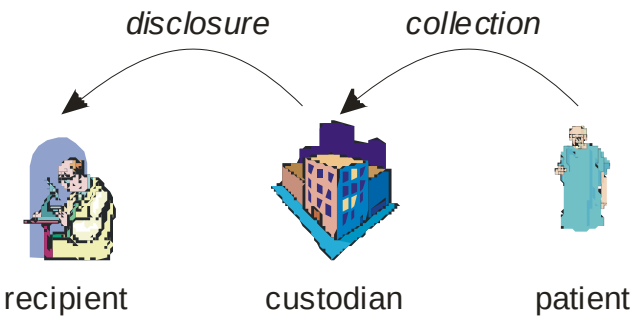

Figure 1: Basic workflow illustrating points at which patient consent can be sought.

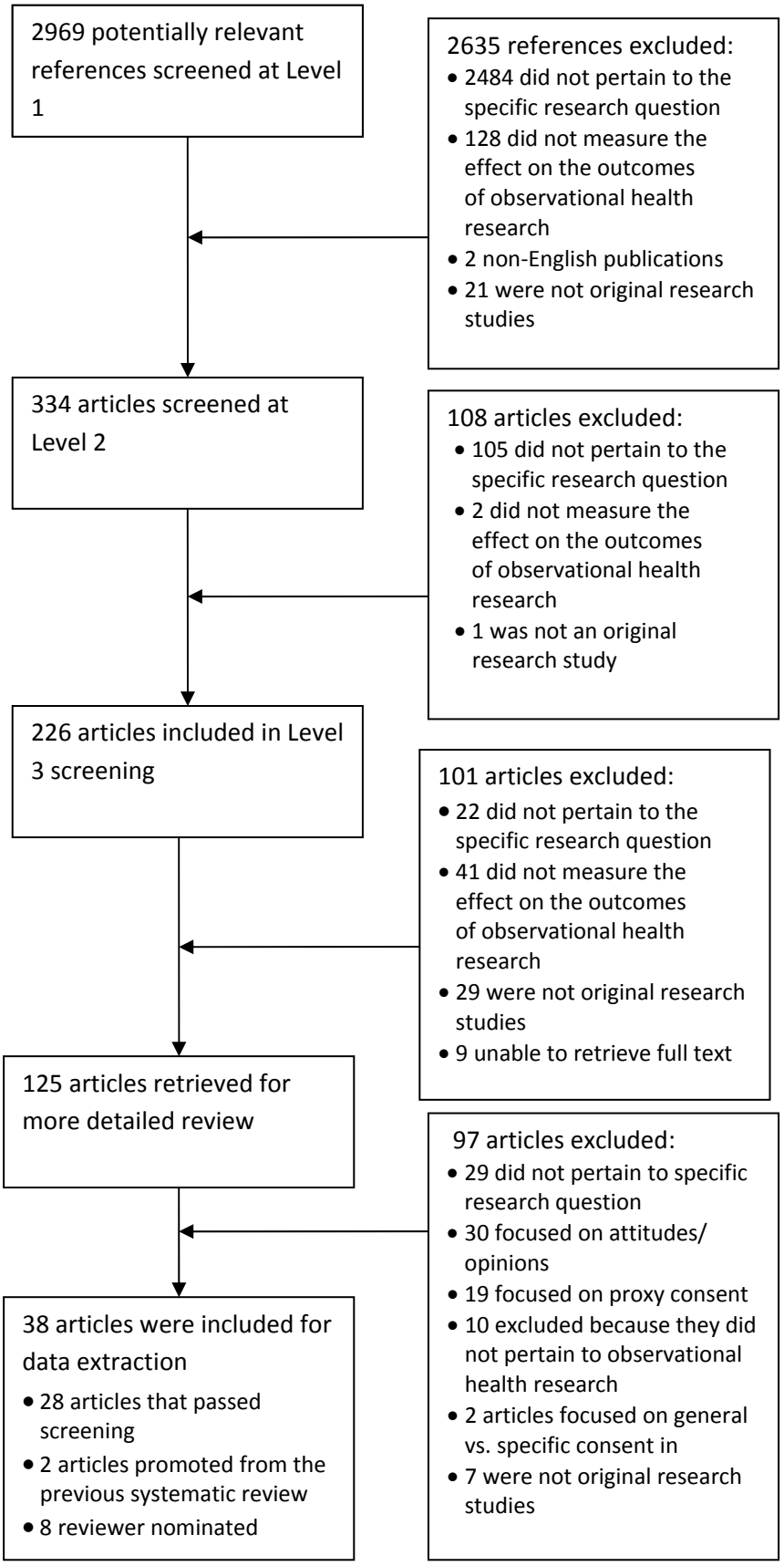

Figure 2: QUOROM flow chart of the systematic review.

A.3.2.1 QUOROM Summary

At levels 1 through 3, articles were excluded during screening if they did not evaluate a privacy regulation, privacy law or consent model. They were also excluded if they did not measure the effect on the outcomes of observational health research, were not published in English, and/or were not original research studies.

At level 4, articles were excluded if they focused on attitudes/opinions concerning consent, focused on proxy consent, compared general vs. specific consent for secondary-use of registry data, did not provide usable data on opt-in vs. opt-out consent or explicit vs. implied consent, did not pertain to observational health research, reported only on response rates to questionnaires, and/or were not original studies. Thirty-seven studies were included for data extraction, from 38 articles. Two articles reported on the same study of a consent-based registry for observational research [23, 24].

The QUOROM flow chart for the review is provided in Figure 1.

A.3.2.2 Impact on Recruitment

Of the 37 studies included for data extraction, 32 reported lower recruitment rates as a result of consent requirements [17, 19-50]. Three studies focusing on opt-in vs. opt-out methods have found that opt-out consent strategies generally produce significantly higher consent rates than opt-in strategies [29, 30, 45]. Junghans, et al, found that 50% of opt-out patients participated, as opposed to 38% in the opt-in group [29]. Trevena, et al, had similar findings with opt-in consent requirements producing a recruitment rate of 47% and opt-out producing a higher recruitment rate of 67% [30]. Lastly, Jacobsen et al, found that when results where analyzed in accordance with opt-in methods, the consent rate was 78%. However, when non-responders were considered to have provided opt-out consent, in accordance with the applicable Minnesota legislation – the law allows for passive consent (opt-out) in cases where patients have been notified about the study by mail on at least two occasions and told that their records may be released should the patient not object— the consent rate increased by 17.5% to 95.5% [45].

Results of these studies are outlined in Table 2.

Study	Sample	Consent rate for opt-in method	Consent rate for opt-out method
Jacobsen [45]	2463	78%	97%
Junghans [29]	510	38%	50%
Trevena [30]	152	47%	67%

Table 2: Recruitment rate for Opt-in vs. Opt-out consent

The 29 studies focusing on explicit consent (opt-in or opt-out) vs. implied consent found that studies with implied consent tended to have elevated recruitment rates. Three of these studies involved a direct comparison between the participation rates of groups requiring explicit informed consent and those instating implied consent for observational health research. These researchers found that participation was higher in the implied condition when informed consent requirements were waived [26-28]. Eleven studies presenting evidence of bias found that a request for explicit opt-in consent to record review, or linkage of study data to medical records decreased participation in surveys and other observational studies [20, 21, 32, 34-38, 40, 43, 50]. Two studies focusing on population-based cohorts both found that the requirement of explicit consent negatively effected the participation rates [33, 42]. Six studies examining participation in registries found that when explicit consent requirements were instated, the result was lower participation by patients [22-24, 39, 41, 44, 48, 49]. Even when opt-out consent methods were employed, the participation rate still decreased in one registry by 6.6% [44]. Three studies found that the requirement of obtaining explicit consent prior to contact from researchers, worked to decrease participation rates [25, 31, 46]. Hollander et al, found that asking for explicit written informed consent led to lower recruitment rates (82%) as opposed to asking for a verbal (uninformed) “okay” (92%) [19]. Cheung et al, had similar findings in their mental health research. When patients were asked for consent, the participation rate decreased by 15.1% [47]. Finally, Beebe and colleagues looked at the impact of consent on survey response rate. They compared a group receiving a HIPAA authorization form (HAF) with a postal survey to that of a group

receiving only the survey questionnaire and found that the group that was sent the HAF had a lower response rate (39.8%) than the group that was sent the survey alone (55%) [17].

Results of these studies are outlined in Table 3 below, and detailed summaries of the study results can be found in Table 5.

Study	Sample	Response Rate	Consent Rate (% of sample)
Al-Shahi [33]	187	59%	59%
Armstrong [27]	1221 (pre), 967(post)	96% in pre-HIPAA period, 35% in post-HIPAA	34% provided written consent in post-HIPAA period
Angus	10,000	20%	[λ] 25%
Beebe [17]	6,939	[*] 55% no HAF, 40% with HAF	40%
Brown [40]	1,612	71.5%	71.5%
Bryant [42]	22,652	100%	52%
Buckley [43]	1,269	69%	45%
Chertow [39]	1,243	100%	51.9%
Cheung [47]	73	85%	85%
Dunn [32]	42,812	65%	32% to follow-up, 42% to medical record review
Dziak [46]	~3000	82% (mean of all sites)	94% (mean of opt-out sites), 63% (opt-in site)
Ford [44]	820	[**] 61%	93%
Harris [36]	2,276	75%	69%
Hess [48]	86	100%	[δ] 55% for RRP & 49% for PSL
Hollander [19]	3,466	87%	92% verbal “okay”, 82% written informed consent
Huang [34]	15,413	95% complete responses	84%
Korkeila [37]	52,739	40%	37%
Krousel-Wood [28]	177	21.5% pre-waiver, 57% post-waiver	21.5%
Nelson [26]	4,647	58% at sites with no consent, 39% with oral consent, 27% with written consent	39% (oral consent), 27% (written consent)
Peat [38]	8,984	68%	25% to follow-up; 27% to medical record linkage
Schwartz/Phipps [23, 24]	2,164	84%	58%
Shah [50]	404	61%	28% (54% of those asked for consent)
Tu [22]	7,108	54% (Phase I/II)	Phase I: 39%, Phase II: 51%
Vates [49]	14,330	35%	28%
Ward [31]	2,804	37%	16%
Woolf [35]	1229	83%	60.5%
Yawn, 1998 [20]	15,997	94%	91%
Yawn, 2002 [41]	391	98%	98%
Young [21]	39,883	52%	49%

[*] HAF stands for HIPAA Authorization Form

[δ] RRP stands for research registry project, and PSL stands for prospective subjects list.

[λ] The response rate is lower than the consent rate because of the requirement to obtain consent prior to participants being sent the survey questionnaire.

[**] This was an Opt-out study which is why the response rate is lower than the consent rate. 54% of those contacted responded with written consent though it was not required, and 6.6% responded in order to opt-out.

Table 3: Recruitment rate for Explicit consent models vs. Implied consent models. Response rate is the percentage of sample that responded either prior to or following consent. Consent rate pertains only to the percentage of the sample that provided explicit consent.

Detailed results are summarized in Table 5.

A.3.2.3 Impact on Bias

Twenty-seven studies found a considerable difference in socio-demographic and/or health features between non-consenters and consenters, as well as between opt-in participants and opt-out participants thereby indicating the presence of selection bias [17, 20-25, 27-30, 32-37, 42-45, 47, 48, 51-55]. The variables most often cited were age, sex, race/ethnicity, marital status, education level, socio-economic status, physical and mental functioning, lifestyle factors, health/disease factors like diagnosis or disease stage/severity, and mortality rate. Table 4 below outlines in which areas each study showed evidence of bias. Two studies in our review found no difference in demographic variables between consenters and non-consenters in observational health research [19, 38].

Study	Age	Sex	Race	Marital Status	Educat-ion level	SES	Health	Life-style factors	Func-tioning
Al-Shahi [33]							X		
Armstrong [27]	X		X	X			X		
Angus [25]	X	X				X			
Beebe [17]							X	X	
Bolcic-Janovic [53]	X	X							
Bryant [42]		X							
Buckley [43]		X					X	X	
Cheung [47]							X		
DiMattio [54]	X		X	X	X	X	X		
Dunn [32]	X	X					X		
Ford [44]							X		
Harris [36]						X	X		
Hess [48]				X			X		
Huang [34]	X			X	X	X			X
Jacobsen [45]	X						X		
Jaskiw [52]	X						X		
Jousilahti [55]	X	X					X	X	
Junghans [29]							X	X	X
Korkeila [37]							X	X	
Krousel-Wood [28]	X	X	X						
Schwartz/Phipps [23, 24]	X	X			X		X		
Stang [51]		X					X		
Trevena [30]					X		X	X	
Tu [22]	X						X		X
Woolf [35]	X	X	X				X		X
Yawn, 1998 [20]	X	X					X		
Young [21]	X			X	X	X	X		

Table 4: Reported evidence of socio-demographic differences between consenters and non-consenters, or opt-in vs. opt-out participants

Fifteen studies examined the age differences of consenters and non-consenters. Of these, 10 studies [20, 21, 25, 27, 28, 35, 45, 53-55], showed that younger patients were more likely to refuse consent or not respond. Conversely, 5 studies found that older patients were more likely not to consent [22-24, 32, 34, 52] .

Sex was another factor that tended to differ between consenters and non-consenters. Of the studies that looked at the sex differences, [20, 23, 24, 28, 35, 43, 51, 53], 7 found that women were more likely to refuse consent than men. Conversely, 4 studies found that women were more likely to give consent than men [25, 32, 42, 55]. Three of the 10 studies found that the consent trends among the sexes tended to reverse in the elderly [25, 32, 53]. Interestingly, the study of survey response rate conducted by Beebe at al, provided contradictory results showing no bias in the consenters group. They found that males were significantly over-represented in the group of respondents that received their survey questionnaire only (in comparison with population values), while no significant over-representation was found in the group in which active consent was sought by way of a HIPAA Authorization Form along with the questionnaire [17].

Of the 4 articles examining race as a factor in consent, all found that African Americans were less likely than Whites to participate in observational health research [27, 28, 35, 54].

Marital status was looked at in 5 studies. Four of these studies found that unmarried people were less likely to consent to participate and/or more likely to discontinue participation [21, 27, 34, 54]. Young et al, found that marital status was also tied to age, with younger consenters being less likely to be married and older consenters being more likely to be married [21]. The fifth study by Hess et al, found that consenters to a research registry project were less likely to be divorced or widowed than non-consenters [48].

Differences in level of education were found in 5 studies. Four studies in our review found that those with lower education levels were less likely to provide active consent [21, 23, 24, 30, 54]. The study by Trevena and colleagues compared opt-in and opt-out consent methods and found that opt-out conditions included more participants with lower levels of education vs. opt-in conditions [30]. Alternately, one study showed that those with higher education levels were less likely to consent [34].

In terms of socio-economic status, 5 studies found a difference between consenters and non-consenters, reporting the status of consenters to be higher than non-consenters [21, 25, 34, 36, 54]. One study found that, in an elderly population, those who were employed or retired were more likely to consent to participate, whereas those participants who discontinued their involvement in the studies were more likely to have a low income [54].

Health factors also appeared to influence consent, as consent patterns varied within studies depending on the patients' health status and/or diagnosis. Twenty-two studies found evidence of bias related to health factors, including mortality [17, 20-24, 27, 29, 30, 32, 33, 35-37, 43-45, 47, 48, 51, 52, 54, 55] . Two studies looked at bias by comparing opt-in participants and opt-out participants [29, 30], and the remaining 18 studies compared consenters and non-consenters. One article looking at consenters in a case-control study found that healthy patients who were approached to become control subjects were less likely to participate (68% participation rate) than case patients with the disease under study (80%) [51]. Another survey-based study found that general health was significantly better in survey respondents who were sent a consent form, as opposed to survey respondents who were sent the questionnaire alone [17]. Conversely, Harris et al, found that consenters generally reported poorer physical and mental health [36]. The severity of the disease was found to be a factor in studies that found consent was greater in patients who had more severe illness/higher stage disease [35, 44]. Conversely, the study by Cheung et al, found that consenters were less severely ill but had a longer duration of illness than non-consenters [47]. In a medical records study by Young et al, it was found that older consenters reported lower use of GP services than did non-consenters [21]. However, in a review of nursing studies focusing on an elderly population, it was found that those with a higher number of hospitalizations were more likely to participate in observational research [54]. In terms of mortality, 5 studies found a higher mortality rate in non-consenters vs. consenters [21, 22, 27, 33, 55].

Lifestyle and risk factors were found to differ between consenters and non-consenters and opt-in vs. opt-out participants in 6 studies. Two studies found that consenters and opt-in participants were more likely to display risk factors, like smoking, family history of disease, etc. [30, 37]. Four studies found the opposite trend with consenters displaying fewer risk factors [17, 29, 43, 55]. Also, in terms of physical and mental functioning, 3 studies found that consent tended to be lower in those with lower mental and/or physical functioning [22, 29, 34] . Woolf et al, in their secondary-use study, found the opposite trend with higher participation in patients who had poorer physical function [35].

Detailed results are summarized in Table 6.

A.3.2.4 Impact on Cost

In our review, 6 studies found that costs increased with an increase in requirements for consent [22-24, 26, 27, 31]. In particular, staffing costs were found to increase due to the demands that obtaining consent can put on research staff [23, 24, 27, 49].

The results on cost are summarized in Table 7.

A.3.2.5 Impact on Time

Three studies found a negative impact of consent requirements on the time needed to conduct a study [22-24, 46]. Tu et al, found that the workload for nurse recruiters was especially heavy due to the requirements of gaining consent from each patient [22]. Schwartz and colleagues found that many personnel hours were required in order to obtain consent from potential patients, while the consent rate in turn was only 58% [23]. Lastly, it was found by Dziak et al, that the time required for their study increased due to variation in IRB review requirements, as well as consequent consent requirements at each study site [46].

The results on time are summarized in Table 8.

Description of Comparisons	Location	Outcome
Comparison of explicit consent vs. implied consent		
Cross-sectional study of patients visiting medical centre (ER, outpatient clinic, and/or hospital) [20]	USA	Consent was requested from 15,997 patients for use of their medical records for research purposes. Of these, 90.6% granted authorization, 3.6% refused, 4.5% were undecided, and 1.3% were not asked. Patients seen in the main office were almost 3 times more likely to explicitly refuse authorization in comparison to those seen in branch offices.
Consent for linkage of survey data to medical record in the Australian Longitudinal Study on Women's Health [21]	Australia	Of the three age cohorts participating in the study, 37% of young women (18-23 years) provided consent to link their Health Insurance Commission (HIC) records with their survey data. The overall consent rate for data linkage was 49.3% (19700 of 39883) of the total group, 59% of middle aged women (45-50 years) and 53% of the older women (70-75 years).
Consent-based patient registry for observational research [23, 24]	USA	In the first 36 months, 2164 eligible patients diagnosed with stroke or traumatic brain injury (TBI) were approached for consent. Of these, 58% (n=1256) consented to be included in the registry, 26% declined, 12% were unsure (maybe) and consented to follow up, and 4% did not come to a decision prior to discharge.
Population surveys in epidemiological research [32]	UK	Researchers analyzed results from seven surveys conducted in the UK. Of the total 42812 subjects sent the surveys, 65% (n=27797) responded. The overall consent rate was 32% of the total sample (75% of responders) authorizing follow-up, and 42% (80% of responders) agreeing to review of their medical records.
Population based cohort study comparing consenters and non-consenters [33]	UK	Of a sample of 187, fifty-nine percent of subjects (n=111) consented to participate.
Cross-sectional study of national health survey with consent for linkage to health record [34]	Taiwan	Of the 15413 subjects, 802 interviewees did not fully complete the survey and were excluded. Eighty-eight percent of the remaining 14611 subjects provided consent for record linkage (83.7% of the total sample), and 12% denied consent.
Consent for inclusion in stroke registry [22]	Canada	Researchers sought consent to inclusion in a stoke registry from 2 samples. In phase I there were 4285 eligible patients and the consent rate was 39.3%. For the second phase, the response rate was 56.6% of 2823 eligible patients.
Consent to examine data for health services	USA	Of the sample of 1229 patients, 83% (n=1106) participated in the survey. Sixty-seven

Description of Comparisons	Location	Outcome
research [35]		percent of survey participants (60.5% of total sample) provided consent for record review.
Survey with consent to linkage with medical record data [36]	UK	The survey response rate was 75% (1704 of 2276). Of the responders, 92% gave consent to have their primary care data linked with their survey answers, and 8% declined.
Survey with consent to use a medical registry-based follow-up [37]	Finland	A total of 19,380 respondents consented to the linkage, 92.65% of all survey respondents. However, researchers suspected that the request for follow-up consent had an effect on overall survey response rate, which was 40% of the original sample.
Longitudinal study with consent to follow-up and record linkage [38]	UK	Eight-thousand nine-hundred and eighty-four eligible patients were mailed a questionnaire, which included a consent form for further contact and medical record review. Of the 8984 eligible patients, 68% (n=6108) responded to the survey but only 34.6% (n=3106) had experienced knee pain in the past 12 months (inclusion criteria). Of those 3106, 71.7% (n=2226) provided consent to follow up & 78% (n=2423) provided consent to medical record review.
Consent to inclusion in Acute Renal Failure registry [39]	USA	Six-hundred and forty-five of the total 1243 patients consulted provided consent (51.9%). Twenty two patients (1.8%) refused to provide consent directly, and 107 (8.6%) patients' families refused to provide consent on their behalf. The remaining 469 (37.7%) of non-participants were excluded due to other reasons such as ineligibility, death, or discharge.
Consent to prospective study of pregnancy outcomes [40]	USA	Of the total patients eligible (n=1612), 28.5% (n=460) did not provide consent. Twenty percent of enrolled patients (n=326) ended their participation before the study finished, and 11% (n=184) became ineligible over the course of the study. In total, 39.8% (n=642) of eligible patients completed the study.
Development of community-based registry with requirement of medical records research authorization [41]	USA	Of all eligible patients with accurate hepatitis c diagnosis, 97.5% (355) provided consent to medical record research and were included in the registry. Nine subjects (2.5%) refused consent to medical records research and consequently could not be included in the registry. Twenty-seven patients were excluded prior to obtaining consent as they were found to be false positives.
Recruitment to population-based cohort with consent to enrollment and record linkage [42]	Canada	Of the 22652 eligible subjects sent the self-administered questionnaire and consent form, 52.4% (n=11865) provided consent for enrollment in the study. Of those who were enrolled, 97% (95.8% of women and 98.1% of men) consented to record linkage with the Alberta

Description of Comparisons	Location	Outcome
		Cancer Registry & Alberta Health and Wellness (the provincial ministry).
Follow up of community cohort for ischaemic heart disease [43]	UK	Follow-up questionnaires & consent forms were sent to 1269 original study subjects. Of these, 69% (n=876) returned the questionnaire and 45% (n=574) provided written consent for further involvement in study.
Comparison of consenters vs. refusers (opt-out consent) for inclusion in Multiple Sclerosis register [44]	UK	After the Data Protection Act was passed (1998), it was recommended that those included in the Leeds MS register should be contacted in order to obtain their consent. Opt-out consent methods were used: patients were asked to reply only if they wanted to be removed from the registry. A total of 6.6% of those included in the register opted-out/refused consent. Of those, 4.1% had MS but wanted their details removed, while 2% replied that they did not have MS, and 3 people asked to be removed due to relocation outside of the area.
Consent to inclusion of data in research registry [48]	USA	In a routine patient questionnaire at a physician office, patients were asked to indicate their interest in having their information included in a research registry (RRP) and a prospective subjects list (PSL) for future research. A consent form was later signed with the physician. Of the 86 completing the questionnaire, 47 (55%) consented to the RRP and 42 (49%) consented to the PSL.
Study of consent to inclusion of data in research registry [49]	USA	Researchers using a clinical tumor registry prior to 2003 endeavored to construct a consent-based research registry following the implementation of HIPAA. Patients were contacted and asked to provide written consent for their personal health information to be included in the registry. Of 14330 patients sent a consent package, 4981 (35%) responses were received, with 66% completing the consent form, 14% not fully completing the form, and 8% refusing. The remaining responses indicated an incorrect address (12%).
Survey with consent to medical record review [50]	UK	Survey questionnaires were sent to 404 patients aged 65-74 years. Half of the questionnaires included a (n=208) request for consent to medical record review. Overall, 245 questionnaires were returned, with another 24 patients identified as deceased or changed address. Of those asked for consent, 130 (62.5% of 208) responded with 113 (54%) consenting and 17 (8%) refusing. One-hundred and fifteen (56% of 206) of those who were not asked for consent responded.

Description of Comparisons	Location	Outcome
Pre-HIPAA vs. post-HIPAA participation analysis [27]	USA	Participation levels differed in the pre and post-HIPAA periods, from 96.4% in the pre-HIPAA period to 34% in the post-HIPAA period when written consent forms were required. Forty percent (n=343) of the 855 patients to whom written consent forms were mailed returned a completed form. Of these, 329 (95.9%) granted consent and 14 (4.1%) refused consent. Consequently, there were 638 non-responders/refusers: no response (n=490), patient not contacted (n=112), mail undeliverable (n=22), and patient refusal (n=14).
Prospective observational study of survey participation [26]	USA	This multi-centre study found different consent requirements between 15 research ethics boards. Seven of the 15 REBs required consent to release contact info: 5 requiring oral consent and 2 requiring written advance permission. Fifty-eight percent of patients at sites without advanced consent requirements completed the survey, in comparison to 39% at sites where oral consent was required, and 27% where written consent was required. Forty-three percent of eligible patients at sites requiring written consent allowed their contact information to be released to researchers.
Non-randomized trial comparing written informed consent vs. verbal (uninformed) consent for emergency department based survey [19]	USA	In this study, 3466 patients were approached with either a standard, written informed consent document, or asked if they could answer “a few routine questions”. Patients approached with written consent forms were more likely to refuse consent vs. patients asked for a verbal “okay”. Overall, 82% of patients asked for written consent participated as opposed to 92% of those for whom written informed consent was not required.
Written consent vs. waiver of consent for release of data to researchers [28]	USA	Participation rates increased from 21.5% in the prewaiver period when opt-in consent was required to 57.4% in the postwaiver period when no prior consent was needed.
Comparison of health survey response from group required to provide consent vs. group with no consent requirement [17]	USA	Eligible patients were randomly assigned to one of 2 groups: Group 1 (n=3470) that was sent the survey only, or Group 2 (n=3469) that was sent the survey along with a HIPAA authorization form (HAF) which was to be signed and returned with the completed survey. After the initial mailing and 2 follow ups, one by mail and one by phone, the overall response rate differed between the groups with a 39.8% response rate in those sent the survey and the HAF vs. a 55% response rate in the non-HAF group.
Examination of recruitment of controls in case-control study [31]	UK	Researchers found that recruitment of controls for this study was detrimentally effected by the implementation of the Data Protection Act. The resulting consent requirements dictated that potential control subjects had to be approached first by their GPs before researchers were able to contact them. Because the case patients in this study often were too debilitated to complete the interview themselves, relatives were interviewed in their stead. The same

Description of Comparisons	Location	Outcome
		procedure was followed for control subjects, which added another level to the consent process. At the end of this process, of the 2804 patients originally written to by their GPs only 16% (n=466) of control patients consented to take part in the study, and a mere 14% (n=397) relatives completed the interview.
Comparison of consenters vs. non-consenters in mental health research [47]	Australia	Of 73 patients, 11 (15.1%) did not participate due to refusal (45.4%), severity of illness (27.3%) or level of aggressiveness (27.3% deemed too aggressive). 62 participants were included in the study.
Consent to participation in survey [25]	UK	Invitation letters and consent forms were sent to 10000 eligible patients prior to the questionnaire. Of these, 2449 (25%) returned a completed consent form and 5 returned the form specifying their refusal to consent. The consequent survey response rate was 80% of consenters (n=1951), but only 20% of the original sample that was approached for consent.
Comparison of prior explicit consent (opt-in or opt-out) and implied consent requirements in multisite health services survey [46]	USA	Fifteen sites were identified to participate in a survey based study to evaluate care in the National Centers of Excellence in Women's Health. Due to variation in consent requirements dictated by the IRB at each site, 4 sites were required to obtain explicit consent prior to contact and 2 sites were required to notify patients (without an opt-in/opt-out option) prior to contact. The remaining sites were not required to obtain prior consent. The 3 sites requiring opt-out consent had a non-consent rate of 1.3%, 5.3%, and 10.6% respectively, whereas the 1 opt-in site had a higher non-consent rate of 36.6%. The requirement of prior explicit consent therefore decreased the number of potential participants at each of these sites, though survey participation rates at these sites remained high (80.7%-87.1% of prior consenters). Sites at which no prior contact was required had response rates between 69.4% and 90.4%.
Comparison of active opt-in vs. opt-out consent		
Opt-in vs. opt-out consent for medical record research [45]	USA	Researchers compared consent rates including non-responders as consenters, and non-responders as having refused consent. Of the 2463 eligible patients, 2023 responded to the mailed request for authorization. The opt-in consent rate was 78% (n=1941), explicit refusal rate was 3.2%, and the non-response rate was 17.5%. When non-responders were considered to be opt-out consenters, in accordance with contemporary Minnesota legislation, the consent rate increased to 96.8%. When non-responders were calculated as opt-in refusers, the refusal rate increased to 20.7%.
Double-blind randomized trial of opt-in vs. opt-out strategies [29]	UK	Recruitment Rate differed between the modes of consent. The opt-in approach produced a 38% recruitment rate, while the opt-out approach produced a higher rate of 50%.

Description of Comparisons	Location	Outcome
Comparison of opt-in vs. opt-out consent methods in randomized controlled trial [30]	Australia	The recruitment rate was lower for the opt-in arm vs. the opt-out arm of this trial. The opt-in arm had a recruitment rate of 47%, compared to the opt-out arm which had a recruitment rate of 67%.

Table 5: Evidence of impact on recruitment rates due to different consent requirements.

Description of Comparisons	Location	Outcome
Comparison of consenters vs. non-consenters and explicit consent vs. implied consent		
Cross-sectional study of national health survey with consent for linkage to health record [34]	Taiwan	The elderly, married, illiterate, lower income and suburban residents were more likely to deny consent. Non-consenters also had lower mean scores in physical and mental domains. Unlike Western studies, Taiwanese Aborigines were significantly less likely to refuse. Unlike other studies, physical & mental health had little impact on consent with only vitality showing a marginally significant influence on non-consent. Gender had no impact.
Written consent vs. waiver of consent for release of data to researchers [28]	USA	Opt-in consent requirements produced participation differences in terms of demographics, and was higher among whites (26.7%) versus blacks (16.1%), men (31.6%) versus women (16.7%), and participants over 75 years old (28.4%) versus those younger than 75 years old (14.6%).
Population based cohort study comparing consenters and non-consenters [33]	UK	Consenters and non-consenters differed in terms of disease factors. Consenters were less likely to present with hemorrhage and more likely to present with seizures than non-consenters. Non-consenters were significantly more likely to be dead or dependent at presentation. At one year follow up, consenters had a lower mortality rate and were less likely to be dependent. This could be due to an inability to obtain consent from adults who died soon after presentation. Surviving consenters were significantly less likely to die and more likely to have a seizure than non-consenters.
Pre-HIPAA vs. post-HIPAA participation analysis [27]	USA	Patients who returned consent forms in the post-HIPAA period were older, married, white, and had a lower mortality rate at 6 months than those who refused consent.
Population surveys in epidemiological research [32]	UK	Consent rate differed by sex, age, and disease symptom. Females, younger people, and subjects reporting the symptom under investigation were more likely to give initial consent. Conversely, when asked for follow up consent, a difference in this trend in terms of sex was found with men being more likely than females to agree to follow up. Also, with advanced age, the likelihood of women consenting decreased whereas the likelihood of men increased.
Comparison of consenters vs. non-consenters for telephone survey of patients and medical record review [53]	USA	Differences in age and gender were found. Men were more likely than women to complete the consent form, whereas respondents under 50 were less likely to return the consent form. A trend in older people was observed where women's response rate decreased with advanced

Description of Comparisons	Location	Outcome
		age while men's response rates increased.
Consent for inclusion in stroke registry [22]	Canada	Patients who participated differed in age, mental alertness and mortality. Participants tended to be younger, more alert at registration, alive at discharge, and to also speak either French or English. In-hospital mortality rate was much lower among patients who were enrolled (6.9%) than those not enrolled (21.7%).
Consent to examine data for health services research [35]	USA	Consenting patients were older, included fewer women and African Americans, and reported poorer physical function. Refusal of consent was associated with more sensitive health problems/ diagnoses. Refusal rates were highest in patients presenting for contraception (46.7%) or with female genital disorders (35.4%). On multivariate analysis, older age, male sex, and lower functional status were significant predictors of consent. Also, those with poorer health were more likely to grant consent.
Cross-sectional study of patients visiting medical centre (ER, outpatient clinic, and/or hospital) [20]	USA	Patient refusal rates differed by diagnosis and were highest among patients visiting for mental health (8.9%), trauma (4.5%), eye care (5.1%), and gynecology (4%). Women were more likely overall to explicitly refuse consent. Those patients who remained undecided were most likely to be women presenting for pregnancy care (15.3%), trauma (9.3%), and musculoskeletal problems (8.9%). Patients seen in the main office were almost 3 times more likely to explicitly refuse authorization than those seen in branch offices. Odds of refusal were also elevated in ER, hospital admission, laboratory or x-ray.
Comparison of consenters in a mental health study vs. non-consenters [52]	USA	Consenters were more likely to be younger and to be diagnosed with schizophrenia. As it is unusual to have a higher consent rate in schizophrenics, it was postulated that low risk research may be more acceptable to people with this disorder. Other demographics were found to play only a minor role.

Description of Comparisons	Location	Outcome
Survey of case-control studies [51]	Germany	Researchers studied participation of controls in all case-control studies in Germany up until March 1997. They found that case patients with the disease under study were more likely to participate than eligible healthy control patients. On average, it was found that 68% of eligible control patients participated in studies vs. 80% of case patients. Recruitment of controls varied by sex, with more men participating than women.
Systematic review of nursing studies [54]	USA	Authors reviewed nursing studies that focused exclusively on women over the age of 65 who were living within in a community setting. When looking at the participants across all studies reviewed, 77% of all participants were found to be white. Of those studies reporting employment of participants, 63% of participants were found to be currently employed or retired. Also, 54% of participants were currently married. One study in the review found that women who had more hospitalizations were more likely to participate. Another study found that non-participants had a lower level of education than participants. In terms of subject retention, women who refused to continue their participation were found to be younger or widowed, and had a low income.
Prospective follow-up study of population based health survey participants and non-participants [55]	Finland	Follow-up study of participants and non-participants from the 1972, 1977, 1982, 1987, and 1992 Finnish population based health surveys assessing risk factor levels for chronic disease. The participants and non-participants were followed up until 2000. Participation rates varied by age and sex, with higher participation among women (87%) vs. men (81.7%) and older age groups vs. younger. Researchers also found a difference in mortality rate between participants and non-participants, with non-participating men having twice and women having 2.5 times greater overall mortality at eight year follow-up. The hazard ratios for disease mortality (i.e., cardiovascular disease and cancer) was higher among non-participants, as were the odds of suicide, violent mortality, smoking related mortality, and alcohol related mortality. The difference in mortality rate between the groups diminished over time until the final 28 year follow-up, but remained significant over time.
Comparison of health survey response from group required to provide consent vs. group with no consent requirement [17]	USA	Researchers found underrepresentation of younger, non-white, and lower educated people over all survey respondents vs. the general population; however, there was no significant difference found between the 2 groups of responders. They did find a difference between responders in regards to sex, with a significantly greater representation of males in the non-consent group vs. the general population, whereas the group requiring consent had no such over-representation. In regards to health, the non-consent group of responders reported lower overall health and a higher number of smokers than the group requiring consent.

Description of Comparisons	Location	Outcome
Consent for linkage of survey data to medical record in the Australian Longitudinal Study on Women's Health [21]	Australia	The consent rate was higher in the older age groups than in the younger cohort. All consenters had higher levels of education and were more likely to possess private health insurance than non-consenters. Young consenters were less likely to be married, whereas older consenters were more likely to be married than non-consenters. The use of GP services was lower in consenters in the mid & older age groups, as opposed to non-consenters. Also, the mortality rate for non-consenters in the older age group was higher than for consenters.
Consent-based patient registry for observational research [23, 24]	USA	Those who provided consent were overall younger in age and had more education than those who refused inclusion in the registry. There was also a greater proportion of men enrolled, and a great number of TBI cases (vs. stroke) in the consenting group.
Survey with consent to linkage with medical record data [36]	UK	There was a higher survey response rate in older people (75+ years), but no demographic differences (i.e. age or sex) between those providing consent and those who did not. However, health differences were noted with consenters reporting poorer mental and physical health. There was also a trend toward more affluent people providing consent, but this was not statistically significant except in the case of owning a car.
Survey with consent to use a medical registry-based follow-up [37]	Finland	Between the consenting and non-consenting responders, consenters reported more risk factors. Namely, the instances of smoking, alcohol use, panic disorder, and the use of tranquillizers were higher in the consenters group than in the non-consenters group.
Recruitment to population-based cohort with consent to enrollment and data linkage [42]	Canada	A higher percentage of women than men consented to data linkage.
Follow-up of community cohort for ischaemic heart disease [43]	UK	Male subjects were more likely to consent to further involvement in research (68.1% of men vs. 60.8% of women). Also, those with lower cholesterol consented more often than those with higher readings. Consent was higher in those with surgical cardiac interventions, and those who had chosen to quit smoking consented more often (73.4%) than smokers (61.4%) and non-smokers (61.6%).
Comparison of consenters vs. refusers (opt-out consent) for inclusion in MS register [44]	UK	In terms of health, differences in disease course were found between refusers and the population. Refusers had a higher percentage of benign relapsing & remitting MS (26.5%) as opposed to the population (11.7%). No patients with relapsing *progressive* MS refused inclusion, whereas 7.1% of the study population presented with this diagnosis. However, it should be noted that not all included records showed a classification of disease course.
Comparison of opt-in and opt-out consent for medical record research [45]	USA	Compared explicit consenters (opt-in and opt-out) to active refusers and found that area of residence, age and health all appeared to effect consent rate. Local residence from within the

Description of Comparisons	Location	Outcome
		area of the study site had a higher rate of declining consent than those living outside of the area. In terms of age, younger patients were more likely to refuse consent than older patients. Health factors also differed between consenters and refusers, namely in terms of diagnoses, patients with more sensitive diagnoses were more likely to refuse consent. Also, those with lower co-morbidity (as denoted by Charlson scores) were more likely to refuse.
Consent to inclusion of data in research registry [48]	USA	Consenters to the research registry (RRP) were compared to non-consenters and it was found that they were less likely to be divorced or widowed, and less likely to present with hypertension. There were no significant differences found between those consenting to be included in the patient subject list (PSL) and those who did not.
Comparison of consenters vs. non-consenters in mental health research [47]	Australia	All participants were schizophrenics, but consenters differed from non-consenters in regards to disease factors. Consenters generally had a longer duration of illness, longer admission, and a greater likelihood of residual schizophrenia. However, they were also less severely ill than non-participants, and less likely to suffer from disorganized schizophrenia.
Consent to participation in survey [25]	UK	Consenters were more likely to be female, less likely to live in deprived areas, and more likely to be older. However, the lowest consent rates were found in the youngest and oldest age groups. Overall, more females than males consented, but in advanced age groups a higher proportion of males consented.
Found no evidence of bias		
Non-randomized controlled trial of written informed consent vs. verbal (uninformed) consent for emergency department based survey [19]	USA	Consenters and non-consenters were found to be similar in characteristics such as age, gender, race, education, independence, substance use, pre-existing medical issues and access to health care.
Longitudinal study with consent to follow-up and record linkage [38]	UK	When compared to the demographics of all eligible patients initially contacted (n=8984), the demographic breakdown of the consenters was similar to that of the study population.
Comparison of opt-in participants vs. opt-out participants		
Double-blind randomized trial of opt-in vs. opt-out strategies [29]	UK	Opt-in patients displayed fewer risk factors then opt-out patients. They were less likely to be smokers, of an ethnic minority, have hypertension, high cholesterol, diabetes and BMI. They also had less treatment for angina and presented with less functional impairment than opt-out patients. However, no significant differences in age, sex, ethnicity, or previous myocardial infarction were found between the groups.
Comparison of opt-in vs. opt-out consent	Australia	Researchers found some socio-demographic differences between the opt-in arm of the trial

Description of Comparisons	Location	Outcome
methods in randomized controlled trial [30]		and the opt-out arm. Particularly, opt-in had more people in active-decision making roles than the opt-out group (75% vs. 45%). Opt-in also was slightly less likely than opt-out to include patients with lower education levels and people who were not screened, but these differences were not statistically significant. The opt-out group was less likely to include people with a family history of colorectal cancer as opposed to the opt-in group (22.7% vs. 10%). The opt-in arm was more likely to recruit people who would be willing to get FOBT screening (93.2% vs. 85%), but less likely to recruit people who had FOBT screening in the past (40.9% vs. 60%) than the opt-out group.

Table 6: Evidence of bias introduced due to opt-in consent requirements.

Description of Comparisons	Location	Outcome
Comparison of explicit consent vs. implied consent		
Pre-HIPAA vs. post-HIPAA participation analysis [27]	USA	Incremental costs for HIPAA compliance was $8704.50 for the first year and $4558.50 annually thereafter. Potential risk of litigation & the associated costs may lead to more conservative interpretations of legislation and increased effort / costs for trials.
Prospective observational study of survey participation [26]	USA	Researchers found that obtaining advanced permission can result in additional costs to the study. The amount of the increase was not specified.
Consent for inclusion in stroke registry [22]	Canada	The total cost of consent related issues in this study totaled $500,000 during the first 2 years of the registry. This was equivalent to 25% of the entire budget.
Examination of recruitment of controls in case-control study [31]	UK	Researchers found the average cost of recruiting each control subject (with extraneous consent requirements) was more than 3 times the cost for each case subject (£1100 for controls vs. £300 for cases).
Consent-based patient registry for observational research [23, 24]	USA	Researchers found that the cost of running the registry was high, due mainly to personnel hours needed for recruitment. However, researchers hope that the cost benefits to studies that use the registry to obtain subjects & information may balance the initial costs incurred.
Study of consent to inclusion of data in research registry [49]	USA	The total cost of the ENT Patient Data Registry project was calculated at $30,888.45 USD. These expenses include $22,855.95 in printing and mailing costs, and $8,032.50 in additional staffing costs.

Table 7: Evidence of increased costs due to opt-in consent requirements.

Description of Comparisons	Location	Outcome
Comparison of explicit consent vs. implied consent		
Consent for inclusion in stroke registry [22]	Canada	Researchers noticed that obtaining consent entailed a heavy workload for nurse recruiters. The project was revamped in phase 2 to decrease work for nurse coordinators, but nurses still spent a median of 40 minutes with each patient or surrogate in Phase 2 in order to obtain consent.
Consent-based patient registry for observational research [23, 24]	USA	Researchers found that the time required for recruitment and obtaining informed consent was high, and consumed a great amount of personnel hours. However, as in the case of costs, the hope is that the time saved for recruitment to future studies may eventually outweigh the initial time spent on recruitment to the research registry.
Comparison of prior explicit consent (opt-in or opt-out) and implied consent requirements in multisite health services survey [46]	USA	Researchers found time required for completion of the study increased due to variation in IRB review at the study between sites. Some IRBs required a no review due to the nature of the study as health services research, whereas some required an expedited review and 5 sites underwent a full review due to concerns about patient privacy. The IRB review times varied between 5 days to 172 days.

Table 8: Evidence of increased time/duration due to opt-in consent requirements.

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