Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review

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Background: It is unclear whether more timely cancer diagnosis brings favourable outcomes, with much of the previous evidence, in some cancers, being equivocal. We set out to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations.

Methods: Systematic review of the literature and narrative synthesis.

Results: We included 177 articles reporting 209 studies. These studies varied in study design, the time intervals assessed and the outcomes reported. Study quality was variable, with a small number of higher-quality studies. Heterogeneity precluded definitive findings. The cancers with more reports of an association between shorter times to diagnosis and more favourable outcomes were breast, colorectal, head and neck, testicular and melanoma.

Conclusions: This is the first review encompassing many cancer types, and we have demonstrated those cancers in which more evidence of an association between shorter times to diagnosis and more favourable outcomes exists, and where it is lacking. We believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of improved survival, earlier-stage diagnosis and improved quality of life, although these benefits vary between cancers.

Symptomatic diagnosis of cancer is important and has been the subject of considerable innovation and intervention in recent years to achieve timelier and earlier-stage diagnosis (Emery *et al*, 2014); the English National Awareness and Early Diagnosis Initiative has made a major contribution to this effort (Richards and Hiom, 2009; Richards, 2009a). We know that patients value timely diagnostic workup, and that later stage at diagnosis is one of the contributory factors to poor cancer outcomes (Richards, 2009b). However, it is less clear whether more timely cancer diagnosis brings favourable outcomes. Systematic reviews in breast cancer reported that delays of 3–6 months were associated with lower survival (Richards *et al*, 1999), and in colorectal cancer it was

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concluded that there were no associations between diagnostic delays and survival and stage (Ramos *et al*, 2007, 2008; Thompson *et al*, 2010). Other reviews have been published for gynaecological cancers (Menczer, 2000), bladder (Fahmy *et al*, 2006), testicular (Bell *et al*, 2006), lung (Jensen *et al*, 2002; Olsson *et al*, 2009), paediatric cancers (Brasme *et al*, 2012a, b) and head and neck cancers (Goy *et al*, 2009; Seoane *et al*, 2012), all with equivocal findings. No review to date has undertaken this work in a range of different cancer types.

Longer time to diagnosis may be detrimental in several ways: a more advanced stage at diagnosis, poorer survival, greater disease-related and treatment-related morbidity and adverse psychological adjustment. Conversely, harm may be caused by earlier detection of cancers without improving survival (lead-time), and detection of slow-growing tumours not needing treatment (over-diagnosis) (Esserman *et al*, 2013). A scoping review, undertaken before the review reported here, showed that observational studies in many cancers reported no association or an inverse relationship between longer diagnostic times and better outcomes (Neal, 2009). We therefore undertook a systematic review of the literature aiming to determine whether there is an association between time to diagnosis, treatment and clinical outcomes, across all cancers for symptomatic presentations only.

MATERIALS AND METHODS

We undertook a systematic review in two phases. The original review was conducted in 2008–10, and the literature from inception of databases to February 2010 was searched; the update was conducted in 2013–14, and the literature from February 2010 to November 2013 was searched. The original review did not include breast or colorectal cancer (because of prior systematic reviews); however, these were included in the update (as we knew of more papers published in these cancers). The review adhered to principles of good practice (Egger *et al*, 2001; NHS Centre for Reviews and Dissemination, 2001). Reporting is in line with the PRISMA recommendations (Moher *et al*, 2009).

A search strategy was developed for Medline (Figure 1) and adapted for other search sources. A range of bibliographic databases were searched for relevant studies. These were as follows:

- MEDLINE, MEDLINE in-process, EMBASE, CINAHL, PsychINFO
- Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, NHS Economic Evaluation database.

Reference lists of studies included in this and previous reviews were hand-searched for relevant studies.

One reviewer screened the titles and abstracts of all records for relevance, and assessed potentially relevant records for inclusion. A second reviewer checked the decisions; disagreements were resolved by discussion or, if necessary, by a third reviewer. A study or analysis was included in the review if it:

- Reported patients with symptomatic diagnosis of primary cancer (screen- and biomarker-detected cancers were excluded).
- Primarily aimed to determine the association of at least one time interval to diagnosis or treatment (patient, primary care, secondary care or a combination), allowing assessment against accepted definitions (Weller *et al*, 2012). The outcomes of interest were any measure of survival or mortality; any description of stage, including extent or severity of disease at diagnosis and response to treatment; or quality of life.

- Was available as full text in English.

Data extraction for all included studies was done by one researcher and checked by another. We extracted data relating to the following:

- Characteristics of included studies: study aim, population, location, setting, definitions of time intervals, data collection methods used and outcome measures.
- Clinical outcomes: included the measure of association, associations of intervals with outcomes and reported interpretation.

1. Exp neoplasms/
2. (time adj4 diagnos$).ti,ab.
3. (time adj4 consult$).ti,ab.
4. (time adj4 treat$).ti,ab.
5. (time adj4 refer$).ti,ab.
6. (time adj4 present$).ti,ab.
7. (time adj4 interv$).ti,ab.
8. (time adj4 therap$).ti,ab.
9. or/2–8
10. (delay$ adj4 diagnos$).ti,ab.
11. (delay$ adj4 consult$).ti,ab.
12. (delay$ adj4 treat$).ti,ab.
13. (delay$ adj4 refer$).ti,ab.
14. (delay$ adj4 present$).ti,ab.
15. (delay$ adj4 interv$).ti,ab.
16. (delay$ adj4 therap$).ti,ab.
17. (delay$ adj4 seek$).ti,ab.
18. (delay$ adj4 care$).ti,ab.
19. (delay adj4 detect*).ti,ab.
20. or/10–19
21. (interval adj4 diagnos$).ti,ab.
22. (interval adj4 consult$).ti,ab.
23. (interval adj4 treat$).ti,ab.
24. (interval adj4 refer$).ti,ab.
25. (interval adj4 present$).ti,ab.
26. (interval adj4 therap$).ti,ab.
27. or/21–26
28. (late adj4 diagnosis).ti,ab.
29. (late adj4 detect*).ti,ab.
30. (late adj4 present$).ti,ab.
31. or/ 28–30
32. (duration adj4 symptom$).ti,ab.
33. Wait$ time$.mp.
34. 9 or 20 or 27 or 31 or 32 or 33
35. 1 and 34
36. limit 35 to (english language and humans and yr="2010 -current")
37. Editorial or letter or practice guideline or biography or case reports or clinical conference or comment or consensus development conference or NIH or guideline or newspaper article or patient education handout
38. Cells[Mesh] or Mass screening[Mesh] or genetic screening[Mesh]) or pregnancy[Mesh]
39. Pharmaceutical preparations[Mesh]
40. Chemical. hw
41. #37 or #38 OR # #39 or #40
42. 36 NOT 41

The original search strategy was found to be too sensitive and produced a large number of non-relevant references. This was revised and refined to capture all relevant articles. The number of databases searched was also more extensive for the original search, but on investigation, it was evident that all included articles had been found on databases subsequently chosen for the updated review.

Figure 1. Search strategy (medline).

Sample representativeness: *Is the sample representative of the relevant cancer patient population? The population may be quite specific, typified by age, stage, ethnicity or other factors.* **Yes:** *only if this is clearly reported* **Can't tell:** *if it's reported in an ambiguous way* **Not reported:** *if it doesn't say* *If none of the above, please qualify with free text (this may be a majority of studies)*
Characteristics reporting: *Was the reporting of participant characteristics complete?* **Yes:** *only if this is clearly and fully reported* **Can't tell:** *is if it's reported in an ambiguous way* **Not reported:** *if it doesn't say* *If none of the above, please qualify with free text (this may be the majority of studies, for example those who just give age and gender)*
Representativeness of participants: *Were participants who participated (or whose data were used) representative of the sample from which they (or it) were sourced?* **Yes:** *only if this is clearly and fully reported* **Can't tell:** *is if it's reported in an ambiguous way* **Not reported:** *if it doesn't say* **Not applicable:** *if all of the sample participated, for example, database study* *If none of the above, please qualify with free text*
Bias minimisation in measurement of symptom duration: *Were steps taken (as stated by the investigators) to minimise and check for, biases and inaccuracies introduced owing to the method used for measurement of symptom duration?* **Yes:** *if clear evidence of this, please list information as free text: MANDATORY* **No:** *if no evidence of this* **Can't tell:** *if unclear (this includes where results may be reported but no mention in methods)*
Independent variable assessment: *Was the assessment symptom duration (explanatory variable) conducted independent of the assessment of the outcome variable?* **Yes:** *if reported as done* **No:** *if clearly reported that same researcher did it* **Not reported:** *if it doesn't say* **Not applicable:** *if the method does not require this to be done, for example, database study*
A priori definition of outcome variable: *Was the outcome variable specified/defined a priori?* **Yes** **No**
Appropriate definition of outcome variable: *Was the outcome variable clearly defined?* **Yes:** *for example, type of stage, type of survival, not necessary to enter detail* **No:** *anything other than yes*
Multivariate analysis: *Was multivariate analysis conducted?* **Yes** **No**
Prognostic adjustment: *Was adjustment for important prognostic factors conducted as part of the analysis?* **Yes:** *if clear evidence of this, (for example: performance status, age, smoking, co morbidity), please qualify with free text MANDATORY* **No:** *if no evidence of this* **Can't tell:** *if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY*
Outlier adjustment for symptom duration: *Was adjustment for outliers conducted as part of the analysis?* **Yes:** *if clear evidence of this, please qualify with free text MANDATORY* **No:** *if no evidence of this* **Not applicable:** *for example if there were no symptom durations greater than 2 years or less for more quickly diagnosed cancers* **Can't tell:** *if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY*
Confounder adjustment: *Was adjustment for confounders (identified in advance of the study) conducted as part of the analysis?* **Yes:** *if clear evidence of this, please qualify with free text MANDATORY* **No:** *if no evidence of this* **Can't tell:** *if unclear (this includes where results may be reported but no mention in methods), please qualify with free text MANDATORY*

We also identified studies (update only 2010–13) that addressed the so-called 'waiting time paradox' (see text).

Figure 2. Bias assessment tool.

- Bias assessment: we envisaged at the outset that there would be considerable variation between included studies in terms of study design, and that many may be of poor quality (Neal, 2009). We therefore considered that the assessment of methodological quality was especially important. However, at that time, there were no widely accepted checklists for checking the quality of prognostic studies, and there was little empirical evidence to support the importance of individual criteria, or study features,

in affecting the reliability of study findings (Altman, 2001). Hence, we decided against the use of quality scoring, and to use a checklist instead of a scale. Judgements on the risk of bias were made according to a number of domains, using a generic list of questions within each domain (Figure 2), based primarily on a framework for assessing prognostic studies (Altman, 2001). For the updated review, and being aware of more recent literature on assessing the quality of prognostic studies, we decided to keep
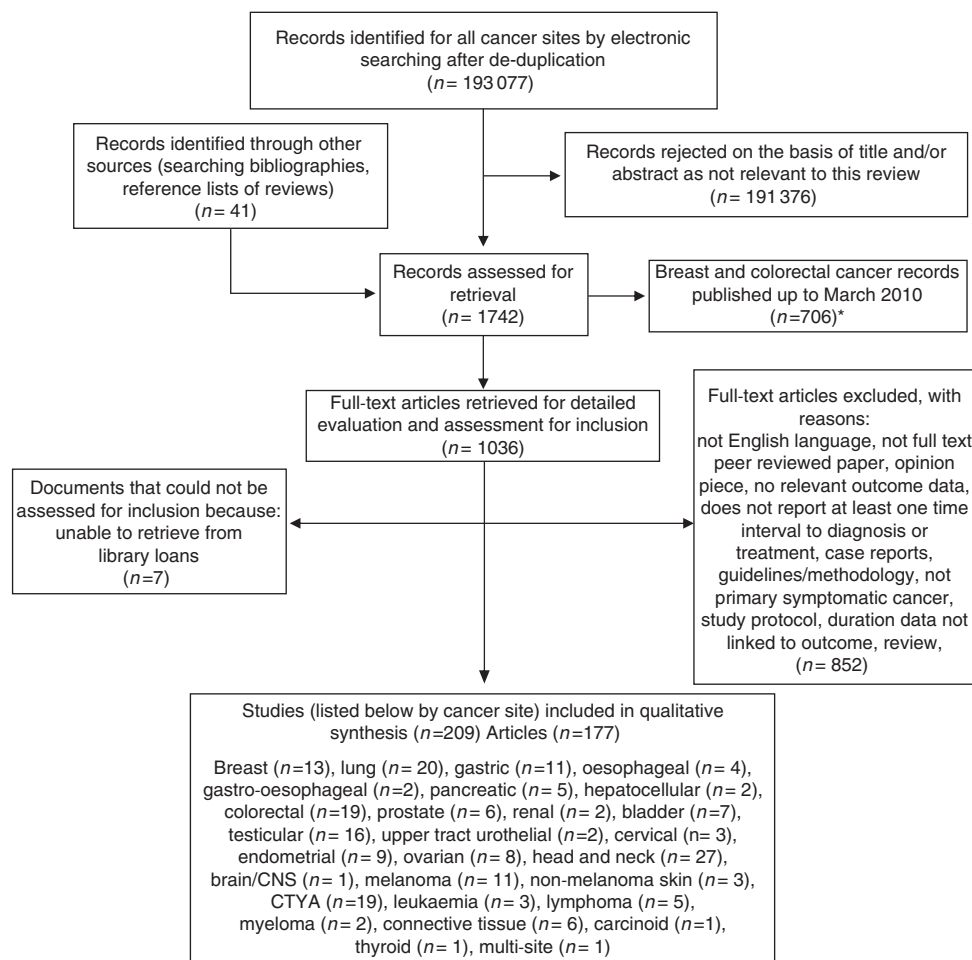
Figure 3. Flow diagram. *Of those breast and colorectal cancer records published up to March 2010 (n = 706) assessed for retrieval, 330 were retrieved and assessed for inclusion but were not included in the evaluation, as systematic reviews on these cancers had been recently published. The follow-up review, covering the period March 2010 to October 2013, included both breast and colorectal cancers in the qualitative synthesis.

the original questions, as they were in line with the new Quality in Prognosis Studies tool (Hayden et al, 2006, 2013). In addition, in the update, we identified studies that addressed the so-called 'waiting time paradox' (Crawford et al, 2002), which were likely to be of higher analytical quality. These were defined as follows: 'articles that undertake an analysis or sub-analysis that specifically includes or excludes patients who are either diagnosed very quickly (e.g., within 4–8 weeks, although this will vary between cancers), or have very poor outcomes (e.g., deaths within a short time after diagnosis, e.g., within 4–8 weeks).' Agreement on inclusion in this subset of articles was done by two members of the study team. This is the 'paradox' caused by the inclusion of patients with aggressive disease who invariably present early and have poor outcomes as a result of the aggressive disease, and is a form of confounding by indication.

- Clinical outcomes: the measure of association, associations of intervals with outcomes and interpretation.

We planned to undertake meta-analysis if there were sufficient homogenous studies reporting a similar outcome measure and the same interval for an individual cancer. Narrative synthesis was undertaken otherwise.

RESULTS

Study selection. The number of studies screened, assessed for eligibility, included and reasons for exclusion are shown in

Figure 3. Of the 1036 records identified for full-text review, 177 articles, reporting 209 studies, met the inclusion criteria and entered the narrative synthesis. A number of the articles reported data on more than one cancer, or more than one interval.

Data collection in the included studies
Definition of time intervals. There were 15 different intervals reported in the included studies (Figure 4).

Clinical and psychological outcomes. Data collection for the outcome measures was predominantly retrospective review of medical records (using a variety of the following: clinical, pathological, histological and imaging) and cancer registries.

Patient questionnaires were used for studies with psychological outcomes. Most studies used various measures of survival (or mortality) and/or stage as outcome measures.

Bias assessment. The bias assessment demonstrates the mixed quality of the studies (Supplementary Online Material). On a positive note, the characteristics and representativeness of the samples were reported in most articles, the definitions and appropriateness of time intervals were well reported and many studies undertook multivariable analysis. However, the representativeness of the samples was not reported in many articles, and few studies undertook confounder adjustment, prognostic adjustment or attempted bias minimisation. Only seven of the articles made an attempt to address the waiting time paradox (Tørring et al, 2011, 2012, 2013; Brasme et al, 2012a, b; Elit et al, 2013; Gobbi et al, 2013; Pruitt et al, 2013). Hence, most studies failed to address the premise of confounding by indication–

	Symptom onset	First seen in primary care	Referral to specialist care	First seen in specialist care	Diagnosis	Treatment

(Figure: horizontal bar chart showing time intervals T1–T15 spanning between the column markers above)

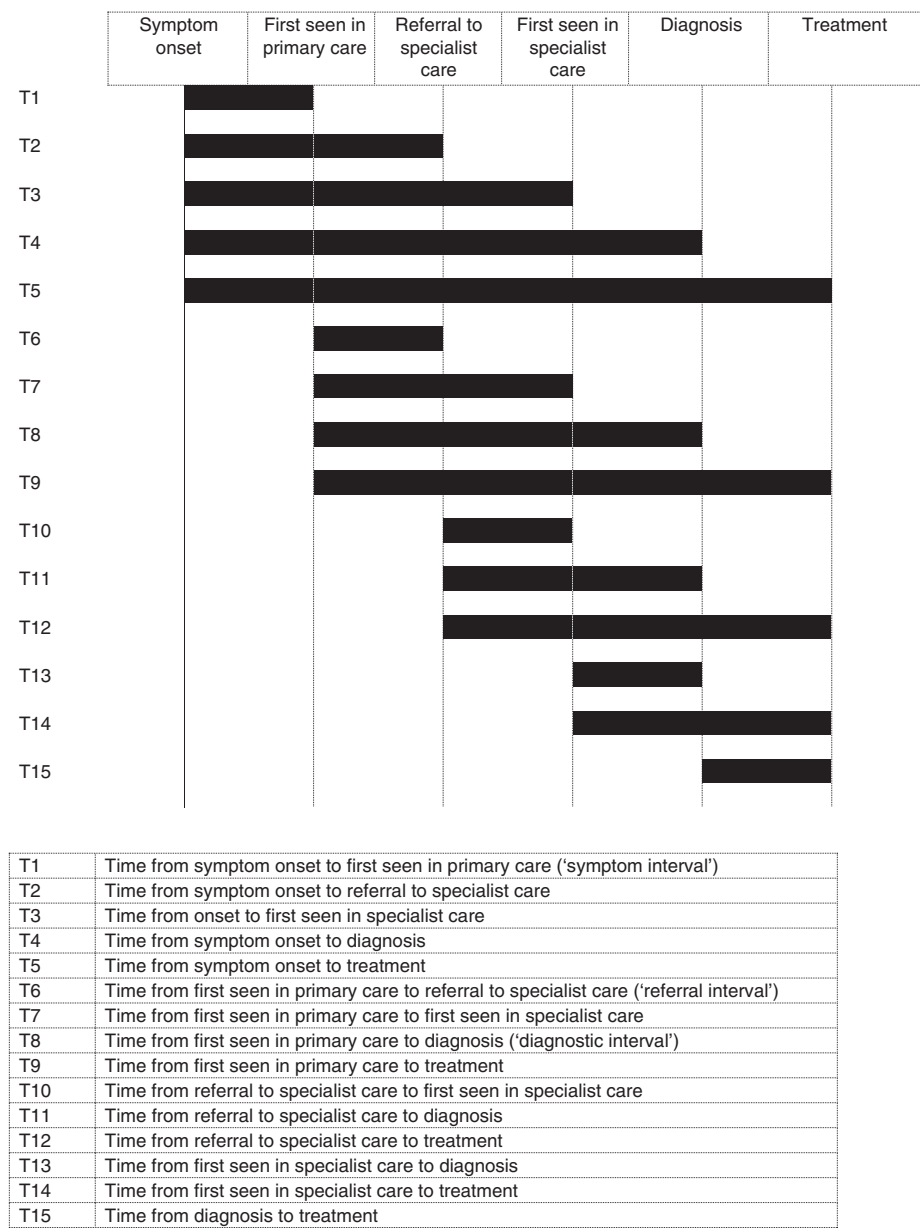|	Definition
T1	Time from symptom onset to first seen in primary care ('symptom interval')
T2	Time from symptom onset to referral to specialist care
T3	Time from onset to first seen in specialist care
T4	Time from symptom onset to diagnosis
T5	Time from symptom onset to treatment
T6	Time from first seen in primary care to referral to specialist care ('referral interval')
T7	Time from first seen in primary care to first seen in specialist care
T8	Time from first seen in primary care to diagnosis ('diagnostic interval')
T9	Time from first seen in primary care to treatment
T10	Time from referral to specialist care to first seen in specialist care
T11	Time from referral to specialist care to diagnosis
T12	Time from referral to specialist care to treatment
T13	Time from first seen in specialist care to diagnosis
T14	Time from first seen in specialist care to treatment
T15	Time from diagnosis to treatment

Figure 4. Definitions of time interval.

that is, the relationship between the diagnostic pathway (and hence the time interval) and prognosis.

Study characteristics. Of the 177 articles included, there were a total of 401 760 participants, with a range of 13 to 147 682 in individual study size (Supplementary Online Material). There were 88 European studies with 23 from the UK, 9 from Italy, 8 from Spain, 8 from the Netherlands, 7 from Denmark, 7 from Finland, 5 from France, 5 from Norway, 3 from Switzerland, 3 from Sweden, 3 from Germany, 2 from Poland and 1 each from Austria, Belgium, Romania, Greece and joint UK/Denmark. There were 18 studies from Asia, with 5 from India, 4 from Japan, 4 from China, 2 from Hong Kong, 2 from Malaysia and 1 from South Korea. There were 59 studies from the Americas, with 47 studies from the USA, 8 from Canada and 4 from Brazil. In addition, there were three from Turkey, two from Israel, two from Australia, one each from New Zealand, Saudi Arabia, Libya, South Africa and one unspecified.

148 were based in specialist care 148 (106 single site, 38 multisite and 4 unspecified), 21 were population based, 3 were set in primary care, 3 database studies, 1 used hospital cancer registry data and 1 was unspecified. Study design varied hugely, and it included prospective and retrospective cohort studies, reviews of medical records, database analyses, patient surveys and interviews. The majority of the studies had retrospective designs.

Synthesis of main findings. The results of individual studies are presented in Supplementary Online Material. No meta-analyses were possible. The results are reported cancer by cancer. Studies are grouped under 'children teenagers and young adults' where they reported at least a significant proportion of participants aged <25 years.

Summaries for each cancer are reported in Table 1. Studies that reported 'positive' associations (i.e., where there was evidence of shorter intervals being associated with more favourable outcomes) are presented first, followed by studies that reported no associations, followed by those that reported 'negative' associations (i.e., where there was evidence of shorter intervals being associated with less favourable outcomes). In each section, studies reporting survival outcomes (or mortality, but for simplicity just referred to as survival in the table) are presented before those reporting stage and other outcomes. A brief narrative for each cancer is provided below.

For breast cancer, four studies reported positive associations, including one of the studies that addressed the waiting time paradox, and was able to demonstrate the effect of different diagnostic intervals on mortality (Tørring *et al*, 2013). The remainder reported no associations.

The lung studies had mixed findings, with similar numbers of studies reporting positive, negative and no associations, across a range of different time intervals. However, one of the studies reporting a positive association with mortality for

diagnostic intervals addressed the waiting time paradox (Tørring *et al*, 2013).

For colorectal cancer, although many studies reported no associations, more studies reported a positive, rather than a negative, association. Indeed, four studies addressing the waiting time paradox were included, three of which reported a positive association (Tørring *et al*, 2011, 2012, 2013) and one a negative association (Pruitt *et al*, 2013). Of the upper gastrointestinal cancers, most studies reported no association, and more reported a

Table 1. Summary results from narrative synthesis, by cancer		
Positive association	**No association**	**Negative association**
Breast		
Survival Diagnostic interval (Tørring *et al*, 2013) Treatment interval (Yun *et al*, 2012; Smith *et al*, 2013) **Stage** Symptom onset to diagnosis (Ermiah *et al*, 2012; Warner *et al*, 2012)	**Survival** Treatment interval (Brazda *et al*, 2010; McLaughlin *et al*, 2012; Eastman *et al*, 2013; Mujar *et al*, 2013; Redaniel *et al*, 2013; Sue *et al*, 2013) **Stage** Treatment interval (Wright *et al*, 2010; Wagner *et al*, 2011) **Other outcomes** Treatment interval and risk of recurrence (Eastman *et al*, 2013)	
Lung		
Survival Diagnostic interval (Tørring *et al*, 2013) Symptom onset to diagnosis (Maguire *et al*, 1994) **Stage** Symptom onset to treatment (Christensen *et al*, 1997) Treatment interval (Brocken *et al*, 2012; Murai *et al*, 2012)	**Survival** Symptom onset to treatment (Annakkaya *et al*, 2007) Patient interval (Loh *et al*, 2006) Diagnostic interval (Loh *et al* 2006; Pita-Fernandez *et al*, 2007; Skaug *et al*, 2011) Treatment interval (Diaconescu *et al*, 2011; Yun *et al*, 2012) Symptom onset to being seen in specialist care (Garcia-Barcala, 2012) **Stage** Patient interval (Yilmaz *et al*, 2008; Tokuda *et al*, 2009) Diagnostic interval(Pita-Fernandez *et al*, 2007; Yilmaz *et al*, 2008) **Other outcomes** Symptom onset to diagnosis and quality of life (Mohan *et al*, 2006)	**Survival** Patient interval (Radzikowska *et al*, 2012) Treatment interval (Gonzalez-Barcala *et al*, 2010) **Stage** Diagnostic interval (Gould *et al*, 2008) Treatment interval (Salomaa *et al*, 2005) Symptom onset to treatment (Myrdal *et al*, 2004) Referral interval (Neal, 2007) First seen in secondary care to diagnosis (Brocken *et al*, 2012)
Gastric		
	Survival Treatment interval (Yun *et al*, 2012) Symptom onset to diagnosis (Maguire *et al*, 1994; Martin *et al*, 1997; Windham *et al*, 2002; Arvanitakis *et al*, 2006) Patient interval (Lim *et al*, 1974) Primary care interval (Lim *et al*, 1974) **Stage** Diagnostic interval (Fernandez *et al*, 2002) Patient interval (Tokuda *et al*, 2009)	**Survival** Symptom onset to diagnosis (Maconi *et al*, 2003) Patient interval (Ziliotto *et al*, 1987) **Stage** Diagnostic interval (Haugstvedt *et al*, 1991)
Oesophageal		
Stage Symptom onset to diagnosis (Martin *et al*, 1997)	**Stage** Diagnostic interval (Fernandez *et al*, 2002) Patient interval (Tokuda *et al*, 2009)	**Stage** Symptom onset to treatment (Wang *et al*, 2008)
Gastro-oesophageal		
Other outcomes Treatment interval and morbidity and in-hospital mortality (Grotenhuis *et al*, 2010)	**Survival** Referral interval (Sharpe *et al*, 2010)	
Pancreatic		
Survival Symptom onset to diagnosis (Gobbi *et al*, 2013) Symptom onset to referral (Raptis *et al*, 2010)	**Survival** Treatment interval (Yun *et al*, 2012) **Stage** Patient interval (Tokuda *et al*, 2009) **Other outcomes** Diagnostic interval and resectability (McLean *et al*, 2013)	

Table 1. (Continued)		
Positive association	**No association**	**Negative association**
Hepatocellular		
Survival Treatment interval (Singal et al, 2013)		
	Stage Patient interval (Tokuda et al, 2009)	
Colorectal		
Survival Diagnostic interval (Tørring et al, 2011, 2012, 2013) Treatment interval (Gort et al, 2010–colon only; Yun et al, 2012–rectal only)	**Survival** Diagnostic interval (Pruitt et al, 2013) Referral interval (Zafar et al, 2011; Currie et al, 2012) Symptom onset to treatment (Thompson et al, 2011) First presentation to diagnosis (Singh et al, 2012) Treatment interval (Roland et al, 2013)	
Stage Treatment interval (Guzman-Laura et al, 2011) colon Referral interval (Valentin-Lopez et al, 2012)	**Stage** Symptom onset to treatment (Terhaar sive Droste et al, 2010; Cerdan-Santacruz et al, 2011; Deng et al, 2012) Referral interval (Ramsay et al, 2012) Treatment interval (Van Hout et al, 2011) Symptom onset to treatment (Van Hout et al, 2011) Patient interval (Cerdan-Santacruz et al, 2011; Van Hout et al, 2011)	**Stage** Treatment interval (Guzman-Laura et al, 2011) rectal
	Other outcomes Patient interval and satisfaction (Tomlinson et al, 2012)	
Prostate		
Survival Diagnostic interval (Tørring et al, 2013) Diagnosis to treatment (O'Brien et al, 2011)	**Survival** Diagnosis to treatment (Korets et al, 2012; Sun et al, 2012) Referral interval (Neal et al, 2007)	
	Stage Diagnosis to treatment (Korets et al, 2012; Sun et al, 2012) Patient interval (Tokuda et al, 2009)	
Testicular		
Survival Patient interval (Hanson et al, 1993) Diagnostic interval (Huyghe et al, 2007; Moul et al, 1990–non-seminoma only) Symptom onset to treatment (Prout and Griffin, 1984; Medical Research Council Working Party, Testicular Tumours, 1985)	**Survival** Patient interval (Fossa et al, 1981) Symptom onset to treatment (Dieckmann et al, 1987) Symptom onset to treatment Meffan et al, 1991) Diagnostic interval (Moul et al, 1990; Harding et al, 1995–seminoma only; Fossa et al, 1981)	
Stage Symptom onset to treatment (Ware et al, 1980; Wishnow et al, 1990) Patient interval (Ware et al, 1980; Chilvers et al, 1989) Diagnostic interval (Bosl et al, 1981; Moul et al, 1990; Huyghe et al, 2007–non-seminoma only) Patient interval (Hanson et al, 1993)	**Stage** Symptom onset to treatment (Dieckmann et al, 1987) Symptom onset to treatment Meffan et al, 1991) Diagnostic interval (Harding et al, 1995)	
Other outcomes Diagnostic interval and chance of complete remission (Akdas et al, 1986); and response to treatment (Scher et al, 1983)	**Other outcomes** Symptom onset to treatment and relapse rate (Napier and Rustin, 2000)	
Renal		
	Stage Patient interval (Tokuda et al, 2009)	**Stage** Symptom onset to treatment (Holmang and Johansson, 2006)
Bladder		
Survival Symptom onset to diagnosis (Hollenbeck et al, 2010) Symptom onset to referral (Wallace et al, 2002)	**Survival** Treatment interval (Gulliford et al, 1991) Referral interval (Wallace et al, 2002) Symptom onset to treatment (Mommsen et al, 1983)	
Stage Diagnostic interval (Liedberg et al, 2003)	**Stage** Symptom onset to diagnosis (Maguire et al, 1994) Patient interval (Tokuda et al, 2009)	
Upper tract urothelial carcinoma		
	Survival Diagnosis to treatment (Waldert et al, 2010; Sundi et al, 2012)	
Stage Diagnosis to treatment (Waldert et al, 2010)		
Cervical		
	Survival Treatment interval (Umezu et al, 2012)	
Stage Patient interval (Fruchter and Boyce, 1981)	**Stage** Primary care interval (Fruchter and Boyce, 1981) Patient interval (Tokuda et al, 2009)	

Table 1. (Continued)		
Positive association	**No association**	**Negative association**
Endometrial		
Stage Symptom onset to diagnosis (Fruchter and Boyce, 1981; Franceschi et al, 1983; Obermair et al, 1996) **Other outcomes** Symptom onset to treatment and quality of life and satisfaction (Robinson et al, 2012)	**Survival** Symptom onset to diagnosis (Menczer et al, 1995) **Stage** Symptom onset to diagnosis (Pirog et al, 1997) Patient interval (Tokuda et al, 2009)	**Survival** Referral to treatment interval (Crawford et al, 2002) Diagnosis to treatment interval (Elit et al, 2013)
Ovarian		
Other outcomes Symptom onset to treatment and quality of life and satisfaction (Robinson et al, 2012)	**Survival** Symptom onset to diagnosis (Nagle et al, 2011) Referral interval (Neal et al, 2007) **Stage** Patient interval (Smith and Anderson, 1985; Tokuda et al, 2009) Symptom onset to diagnosis (Fruchter and Boyce, 1981; Menczer et al, 2009; Nagle et al, 2011)	**Stage** Symptom onset to diagnosis (Lurie et al, 2010)
Head and neck		
Survival Patient interval (Koivunen et al, 2001–pharyngeal; Teppo and Alho, 2008–pharyngeal and laryngeal cancers (separately)) Diagnostic interval (Alho et al, 2006–head and neck unspecified; Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–laryngeal) Symptom onset to treatment (Hansen et al, 2004–laryngeal) Treatment interval (Sidler et al, 2010–nasopharyngeal) **Stage** Patient interval (Kumar et al, 2001–oral; Brouha et al, 2005b–oral and pharyngeal cancer (separately); Lee et al, 1997–nasopharyngeal; Sheng et al, 2008–nasopharyngeal; Tromp et al, 2005–head and neck unspecified; Tokuda et al, 2009–head and neck unspecified; Tromp et al, 2005–head and neck unspecified) Diagnostic interval (Allison et al, 1998–aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal) Symptom onset to diagnosis (Allison et al, 1998–aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal) Symptom onset to referral (Pitchers and Martin, 2006–oropharyngeal) **Other outcomes** Diagnostic interval and risk of recurrence (Teppo et al, 2005–laryngeal)	**Survival** Patient interval (Teppo et al, 2003–laryngeal; Teppo and Alho, 2008–tongue) Diagnostic interval (Seoane et al, 2010–oral; Teppo and Alho, 2008–pharyngeal and tongue (separately); Koivunen et al, 2001–pharyngeal) Symptom onset to diagnosis (Wildt et al, 1995–oral) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) Treatment interval (Caudell et al, 2011–head and neck unspecified; Brouha et al, 2000–laryngeal) **Stage** Patient interval (Allison et al, 1998–upper aerodigestive tract; Al-Rajhi et al, 2009–nasopharyngeal; Brouha et al, 2005a–laryngeal cancer; Wildt et al, 1995–oral; Teppo et al, 2009–vestibular schwannoma) Diagnostic interval (Teppo et al, 2009–vestibular schwannoma; Ho et al, 2004–oropharyngeal) Symptom onset to diagnosis (Miziara et al, 1998–laryngeal; Scott et al, 2005–oral) Symptom onset to referral (Vernham and Crowther, 1994 head and neck unspecified) Symptom onset to treatment (McGurk et al, 2005–head and neck unspecified) **Other outcomes** Patient interval and risk of recurrence (Teppo et al, 2005–laryngeal)	
Brain/CNS		
Other outcomes Symptom onset to diagnosis and progressive neurological deterioration (Balasa et al, 2012)		
Melanoma		
Survival Patient interval (Temoshok et al, 1984, Montella et al, 2002) Diagnostic interval (Temoshok et al, 1984; Metzger et al, 1998; Montella et al, 2002; Tørring et al, 2013) **Stage** Patient interval (Richards et al, 1999) Symptom onset to diagnosis (Helsing et al, 1997)	**Stage** Patient interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Carli et al, 2003; Baade et al, 2006) Diagnostic interval (Cassileth et al, 1982, Schmid-Wendtner et al, 2002; Baade et al, 2006) Symptom onset to diagnosis (Krige et al, 1991; Baade et al, 2006)	
Non-melanoma skin		
Stage Patient interval (Tokuda et al, 2009) **Other outcomes** Symptom onset and presentation to specialist care and increase in tumour size (Alam et al, 2011)	**Other outcomes** Symptom onset to treatment and larger lesions (Renzi et al, 2010)	

Table 1. (Continued)		
Positive association	**No association**	**Negative association**
CTYA		
Survival Symptom onset to diagnosis (Marwaha *et al*, 2010b–leukaemia; Ferrari *et al*, 2010–soft tissue sarcomas) First seen in specialist care to diagnosis (Marwaha *et al*, 2010a–leukaemia)	**Survival** Symptom onset to diagnosis (Kameda-Smith *et al*, 2013–soft tissue sarcomas; Sethi *et al*, 2013–posterior fossa tumours) Diagnostic interval (Lins *et al*, 2012–leukaemia; Crawford *et al*, 2009–primary spinal cord tumours) Patient interval (Yang *et al*, 2009 –osteosarcoma) Symptom onset to diagnosis (Brasme *et al*, 2012a, b–medulloblastoma; Loh *et al*, 2012–paediatric solid tumours; Butros *et al*, 2002–retinoblastoma)	**Survival** Patient interval (Kukal *et al*, 2009–brain tumours) First symptom to treatment (Erwenne and Franco, 1989–retinoblastoma)
Stage Diagnostic interval (Wallach *et al*, 2006–retinoblastoma)	**Stage** Patient interval (Yang *et al*, 2009 –osteosarcoma; Simpson *et al*, 2005–Ewing's sarcoma) Symptom onset to diagnosis and eye loss (Butros *et al*, 2002–retinoblastoma)	**Stage** Diagnostic interval (Crawford *et al*, 2009–primary spinal cord tumours; Halperin *et al*, 2001–medulloblastoma; Bacci *et al*, 1999–Ewing's sarcoma)
Other outcomes Symptom onset to treatment and extra-ocular disease (Erwenne and Franco, 1989–retinoblastoma)	**Other outcomes** Patient interval and eye loss (Goddard and Kingston, 1999–retinoblastoma) Treatment interval and relapse rate (Wahl *et al*, 2012–leukaemia)	
Leukaemia		
	Survival Diagnostic interval (Friese *et al*, 2011 (chronic lymphocytic)) Symptom onset to diagnosis (Prabhu *et al*, 1986 (chronic myeloid)) Treatment interval (Bertoli *et al*, 2013 (acute myeloid))	
Lymphoma		
	Survival Symptom onset to diagnosis (Jacobi *et al*,2008 (follicular); Maguire *et al*, 1994 (unspecified); Norum, 1995 (Hodgkin's))	**Survival** Symptom onset to diagnosis (Kim *et al*, 1995; Foulc *et al*, 2003 (both Sezary syndrome))
Myeloma		
Survival Symptom onset to diagnosis (Kariyawasan *et al*, 2007) **Other outcomes** Symptom onset to diagnosis and complications at diagnosis (Kariyawasan *et al*, 2007; Friese *et al*, 2009)		
Connective tissue		
Survival Symptom onset to treatment (Ruka *et al*, 1988 (soft tissue sarcoma)) Symptom onset to diagnosis (Saithna *et al*, 2008 (soft tissue sarcoma)) Symptom onset to diagnosis (Nakamura *et al*, 2011 (soft tissue sarcoma))	**Survival** Symptom onset to diagnosis (Rougraff *et al*, 2007 (soft tissue sarcoma; Wurtz *et al*, 1999 (osteosarcoma)) **Stage** Symptom onset to diagnosis (Bacci *et al*, 2002 (osteosarcoma))	
Carcinoid		
	Survival Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004) **Stage** Symptom onset to diagnosis (Toth-Fejel and Pommier, 2004)	
Thyroid		
	Stage Patient interval (Tokuda *et al*, 2009)	
Multisite		
Survival Diagnostic interval (Tørring *et al*, 2013 (breast, lung, colorectal, prostate and melanoma combined)		

negative, rather than a positive, association. For pancreatic cancer, two of the five studies reported a positive association, one of which addressed the waiting time paradox (Gobbi *et al*, 2013). The other three studies reported no association.

Two of the prostate studies reported a positive association for survival/mortality, one of which addressed the waiting time paradox (Tørring *et al*, 2013); the others reported no association. Two of the bladder studies reported a positive association; the others reported no association. For testicular cancer, 15 studies reported positive associations, and the remainder had no associations.

For gynaecological cancers, of the four studies examining cervix, one reported a positive association; the others reported no association. For endometrial and ovarian cancers, there were similar numbers of studies with positive, negative and no associations. One of the endometrial studies that reported a negative association addressed the waiting time paradox (Elit *et al*, 2013).

For head and neck cancers (pharyngeal, laryngeal, oral and others), there were a large number of studies and these were equally divided between those reporting a positive association and those reporting no association. No studies reported a negative association.

For melanoma, eight studies reported positive associations, one of which addressed the waiting time paradox (Tørring et al, 2013); the remainder reported no associations. For non-melanoma skin, two studies reported positive associations and one reported no association.

There were a large number of studies covering the various cancers in children, teenagers and young adults. The findings of these were very mixed, with the biggest group showing no associations, and smaller but similar number of studies reporting both positive and negative associations. One of the 'no association' studies addressed the waiting time paradox (Brasme et al, 2012a, b).

For lymphoma, three studies reported no association or a negative association. For leukaemia, the three studies reported no associations. There were only two studies in myeloma, although both of these reported positive outcomes. For the various connective tissue cancers, three studies each reported a positive association and no association. The other cancer groups (brain/central nervous system, carcinoid, hepatocellular, renal, thyroid, upper tract urothelial carcinoma and multisite) only had one or two included studies.

DISCUSSION

Summary of main findings. This review is unique in that it has assessed the literature for a range of different cancer types, and hence we are able to make recommendations for policy practice and research that are not limited to one cancer (or group of cancers). The number of included studies in this review has shown the importance of this question to patients, clinicians and researchers. However, even within specific cancer types, there is only moderate consensus as to the nature of any associations between various time intervals in the diagnostic process and clinical outcomes, with some studies showing no associations, some studies showing better outcomes with shorter time intervals and some the opposite. There are more reports of an association between times to diagnosis and outcomes for breast, colorectal, head and neck, testicular and melanoma, with reports from a smaller number of studies for pancreatic, prostate and bladder cancers. The time intervals in the studies varied, making it impossible to draw consensus as to which intervals may be more, or less, important. Moreover, the methodological quality of many of these papers is mixed, despite a recent consensus paper on design and reporting of such studies (Weller et al, 2012). There is some evidence from papers published more recently that address the waiting time paradox in their analyses (Tørring et al, 2011, 2012, 2013; Brasme et al, 2012a, b; Elit et al, 2013, Gobbi et al, 2013, Pruitt et al, 2013), with most, but not all, of these reporting longer intervals being associated with poorer outcomes, particularly mortality. This is important and begins to provide more robust evidence about the relationship between time to diagnosis and outcomes.

Findings within the context of the literature. The previous cancer-specific reviews (Menczer, 2000; Jensen et al, 2002; Bell et al, 2006; Fahmy et al, 2006; Ramos et al, 2007, 2008; Goy et al, 2009; Olsson et al, 2009; Thompson et al, 2010; Brasme et al, 2012a, b), with the exception of the breast cancer (Richards et al, 1999), and to a lesser extent head and neck (Seoane et al, 2012), have been largely equivocal, probably because of the poor quality of the included studies. Our findings are largely in keeping with these

reviews, although we have provided much more evidence than previous reviews for testicular cancer (Bell et al, 2006) and head and neck cancers (Goy et al, 2009). We have also identified more recent and probably higher-quality papers providing better evidence for colorectal cancer than covered in previous reviews (Ramos et al, 2007, 2008; Thompson et al, 2010). We provide review findings for the first time for many cancers. We are also aware of further articles being published since the end date of our review. For example, one of these replicated the methods of one of the papers in our review (Tørring et al, 2011) on a sample of 958 colorectal cancers in Scotland, and reported that longer diagnostic intervals did not adversely affect cancer outcomes (Murchie et al, 2014). Another has reported that time to diagnosis in 436 Ewing tumours in France was not associated with metastasis, surgical outcome or survival (Brasme et al, 2014). One of our main findings, of the poor quality of reporting of time to diagnosis studies, replicates the findings of a recent paediatric systematic review (Launay et al, 2013).

Strengths and weaknesses. This is the largest and most comprehensive review in this field, and the first 'all-cancer' systematic review. The huge heterogeneity in both the outcomes and the time intervals used, within each cancer site, precluded meta-analyses. Another systematic review has recently reported similar difficulty in comparisons between studies (Lethaby et al, 2013). As previously stated, the review only contains studies in colorectal and breast cancer for 2010–13, and only these studies identified during the second round of searches were assessed to determine whether their analyses addressed the waiting time paradox. Survival, or mortality, is the most objective outcomes for these studies. However, many of the included studies in the review reported stage, or some other proxy. This may explain why stage and survival outcomes differ. Stage categorisation also varied, and some of the studies may be affected by post-hoc upstaging. A further problem with the literature is that of confounding by indication. Symptoms of more advanced cancer are likely to present differently and be investigated more promptly, as are patients presenting with so-called 'red-flag' symptoms. We were unable to assess for publication bias; indeed, if there was any publication bias, we cannot predict in which direction this would act.

Implications for policy, practice and research. Our main conclusion from this review is that we believe that it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients in terms of earlier-stage diagnosis, improved survival and improved quality of life. The amount of benefit varies between cancers; at present, there is more evidence for breast, colorectal, head and neck, testicular and melanoma, with evidence from a smaller number of studies for pancreatic, prostate and bladder cancers. There is either insufficient evidence or equivocal findings in the other cancers. The findings need replicating in using similar analytical methods, ideally also to address how much of a difference expedited diagnosis of different cancers would make on outcomes, and at which points in the diagnostic journey matters most. Until we have well-designed and well-analysed prospective studies to answer this question, it is difficult to determine the likely effect of interventions to reduce patient and diagnostic intervals on outcomes. This knowledge would inform the development of targeted intervention studies, to improve outcomes.

Hence, we recommend that policy, and clinicians, should continue the current emphasis on expediting symptomatic diagnosis, at least for most cancers. This can be achieved by clinicians having a high index of suspicion of cancer, the use of diagnostic technologies and rapid access to diagnostic investigations and fast-track pathways for assessment (Rubin et al, 2014). Finally, we recommend the need for more high-quality research in

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Box 1. Key quality criteria for studies that examine the relationship between time intervals in cancer diagnosis and outcomes.

Good studies will report the definition of intervals in compliance with definitions in the Aarhus statement (Weller *et al*, 2012). The most common intervals reported are as follows:

- Patient interval – the time from when bodily changes and/or first symptoms are noticed to presentation of this change or symptom to a health care professional
- Diagnostic interval – the date from first presentation to a health care professional to diagnosis
- Referral interval – the date from referral to specialist care to being seen in specialist care

Good studies will report key dates in the diagnostic journey in a standardised way, with a full description. This includes, for example, the following:

- Dates when patients first notices bodily changes or symptoms and when they decide to seek help
- Date of first presentation of potential cancer symptom – including how such symptoms were defined
- Date of diagnosis – clear reporting of how this date was obtained and what date it actually represents (e.g., date of tissue diagnosis, date when patient informed)
- Dates of referral / investigation – including definitions of which were included and why

Good studies will fully describe appropriate data collection methods for time intervals. These will vary by interval, and different approaches to data collection (e.g., interviews, questionnaires, medical records, database studies) will give different answers. Data collection from patients is preferred for studies measuring patient intervals. Precise details regarding data collection methods are preferred.Good studies will fully describe and justify outcome measures. Mortality or survival is preferred, but some measure of stage (or other measure of disease severity or treatment modality) is also a useful endpoint. Studies capturing patient experience and quality of life and psychological outcomes are also needed.

Good studies will use a design that addresses bias and confounding (including confounding by indication); this includes measures to address the waiting time paradox.

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the area for a number of reasons. First, we suspect that many clinicians continue to believe that there are no associations between time and clinical outcomes.

A considerable number of studies fail to address basic issues of bias and thus equate the absence of evidence with evidence of absence. Second, it is likely that more timely diagnosis may have a greater or lesser impact between different cancers. This is important to ascertain, because it will inform policy and practice. We recommend, where possible, re-analysis of pooled (and similar) data from some of the studies included in this review, and new studies using linked data sets, across all cancers, such that similar analyses can be conducted between cancers. We also recommend that such studies should ideally focus on survival or mortality as the outcome, as this is the 'gold-standard' outcome, although stage is also a valuable end point. There is also a dearth of studies reporting patient experience; we therefore recommend further work that examined the relationship between patient perceptions of 'delay' and quality of life and psychological outcomes. Suggested key quality criteria for future studies are summarised in Box 1. Other work should focus on the organisation and function of health services, and subsequent time intervals and outcomes. Furthermore, we recommend that, wherever possible, this work

should be conducted and reported in keeping within the recommendations of the Aarhus Statement (Weller *et al*, 2012).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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