Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Synthesis
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In response to an enquiry from the Scottish Government Cancer Waiting Times Review Implementation Group

The association between cancer outcomes and time intervals to diagnosis and treatment

What were we asked to look at?

To inform an ongoing clinical review of cancer waiting times in Scotland we were asked to summarise the published evidence on the association between time intervals to diagnosis and treatment and cancer outcomes.

Why is this important?

It is important to understand the likely impact of variations in cancer waiting times across various cancer types to help ensure optimal outcomes for patients and inform planning and policy for cancer services in Scotland.

What was our approach?

This Evidence Synthesis provides an update to a comprehensive 2015 systematic review of time to diagnosis and treatment and its effects on cancer outcomes.

As a full update would require review of a very large number of primary studies it was agreed that we should focus on identifying and summarising the findings of secondary evidence published since the 2015 systematic review search was carried out.

What next?

The findings will be considered by the Scottish Government Cancer Waiting Times Review Implementation Group.

Key findings

- It is not possible to reach clear conclusions on the association between cancer outcomes and time intervals to diagnosis and treatment due to heterogeneity across the evidence base, both in terms of time intervals examined and the outcomes that are measured. Studies are mainly retrospective and at high risk of confounding by indication, for example where patients with severe symptoms are diagnosed and treated very quickly but have poor outcomes due to aggressive disease.
- Well conducted systematic reviews were identified for the following cancer types:
    - **head and neck cancers -** two systematic reviews reported that longer intervals to diagnosis and from diagnosis to treatment were associated with poorer survival outcomes. A referent interval of 30 days was commonly used in studies.
    - **colon cancer -** four out of five studies included in a systematic review reported no association between longer intervals from diagnosis to initiating surgical treatment and overall survival outcomes. Interval categories analysed ranged from >31 days to >60 days.
    - **prostate cancer -** most studies identified in a systematic review did not find an association between longer time to treatment (variously defined) and oncologic outcomes, such as biochemical recurrence and cancer stage. None found a relationship with metastases or reduced survival. The majority of studies only included low risk patients.
- Systematic reviews on bladder cancer and non-small cell lung cancer are in preparation for publication.
- Peer reviewers and collaborators in the development of this Evidence Synthesis highlighted that the patient interval - from initial awareness of symptoms to first presentation/clinical appearance – may be an important contributor to cancer outcomes.

Contents

Introduction

Policies around timeliness of cancer diagnosis and care should be informed by evidence for improved patient outcomes and patient experience[1]. Rapid diagnosis and early treatment initiation aims to minimise the opportunity for tumour growth and spread, and protect the viability of treatment options. The natural development of different cancers, however, means that a standard waiting times policy for all tumour types may not be a rational approach and may lead to unnecessary stress on cancer services and provoke unnecessary distress and anxiety in patients[2, 3].

A clinical review of cancer waiting times (CWT) standards in Scotland noted the lack of clear evidence behind the current waiting times standards and recommended a review of evidence for making CWT standards timings variable according to tumour biology[4].

Research question

What is the published secondary evidence on the association between cancer outcomes and time intervals to diagnosis and first treatment?

Literature search

A systematic search of Medline, Embase, and PsychInfo databases was carried out on 11 June 2019 to identify systematic reviews, meta-analyses and other the secondary evidence.

Concepts used in all searches included: cancer, time/delay/interval to diagnosis/treatment. A full list of resources searched and terms used are available on request. The search was limited to English language studies published between 2013 and June 2019. The SIGN systematic reviews filter was used for Medline and Embase.

NHSScotland waiting time standards

NHSScotland presently has two standards around cancer diagnosis and treatment[5]:

A 62 day standard from receipt of referral to start of treatment for newly diagnosed primary cancers. This applies to:

- Patients urgently referred with a suspicion of cancer by a primary care clinician
- Screened positive patients referred through a national cancer screening programme
- Direct referral to hospital where the signs and symptoms are consistent with the cancer diagnosed as per the Scottish Referral Guidelines e.g. self-referral to A&E

A 31 day standard from decision to treat to start of treatment for newly diagnosed primary cancers (whatever their route of referral).

Although the patient interval (from initial awareness of symptoms to first presentation/clinical appearance) is outside of these standards it may be an important determinant of cancer outcomes.

CWT performance is monitored across the following cancer types:

- Breast
- Colorectal
- Head and neck
- Lung
- Lymphoma
- Ovarian
- Melanoma
- Upper Gastro-Intestinal
- Urological
- Cervical

In the first quarter of 2019, 81.4% of 3,692 eligible patients started treatment within the 62 day standard and 94.9% of 6,245 eligible patients started treatment within the 31 day standard[5].

A study using data from NHS England explored the effects on one year survival of meeting or not meeting similar standards highlighted the limitations of waiting times data and the difficulties in assessing the effectiveness of standards with respect to improving patient outcomes[6]. Survival for ovarian, lung and colorectal cancer patients was worse for those for whom the targets were met which may indicate that treatments with palliative intent (in the patients with worst prognosis) are initiated more quickly than those planned with curative intent. The study authors concluded that while patients may benefit psychologically from timely treatment, one-year survival is not a useful measure for evaluating the targets.

Defining time intervals

The majority of the studies included in this Evidence Synthesis note the difficulties of reaching conclusions owing to the range of, and variation in definitions of, time intervals across the literature.

Although not widely adopted to date, a series of recommendations to improve the quality, transparency, consistency and comparability of studies of diagnostic intervals in symptomatic cancer was developed by an international Consensus Working Group (CWG) in November 2009[7]. Known as the Aarhus Statement, it recommends that definitions of time intervals be standardised across studies with a move away from the use of terminology focused on the concept of 'delays' which are heterogeneously defined across the published evidence. A checklist was also developed to inform research planning and assess how well studies measure and map patient cancer journeys.

Literature review - secondary evidence

All cancers

The starting point for this Evidence Synthesis was a comprehensive systematic review published in 2015 by Neal et al which investigated whether increased time to diagnosis and treatment in symptomatic cancer was associated with poorer clinical outcomes[8]. Inclusion criteria were for studies in full text and English language examining:

- Symptomatic presentation/diagnosis (screening and biomarker detected cancers were excluded)
- The effect of at least one time interval to diagnosis or treatment (15 different specified time intervals were identified across the studies)
- Outcomes of survival, cancer stage, response to treatment or quality of life.

The literature search (carried out in 2013), identified 209 studies within 177 publications. Most studies were retrospective and based on patient records. Few studies undertook adjustment for confounders or prognostic factors. When the literature from 2010 onwards was examined, only seven publications explicitly addressed the waiting time paradox which is a form of confounding by indication, where patients with severe symptoms are diagnosed and treated very quickly but have poor outcomes due to aggressive disease. Sub analysis to examine the effects of including or excluding such cases would be expected in the most robust studies.

Table 1 summarises the information presented in the Neal et al review for all cancers where more than two studies were identified. No meta-analyses were possible so the authors categorised and described the findings of each study. The definition of intervals varied greatly and, as well as service intervals (time to seeing a specialist, diagnosis and treatment), included the patient interval between onset of symptoms and first visit to primary care. Fifteen different time intervals were identified across studies and defined in the review. Cancer outcomes were most frequently defined as survival or cancer stage although outcomes such as chance of complete remission, risk of recurrence and quality of life were examined in some studies.

Study findings were mapped according to positive, negative or no association between shorter time interval and outcomes. Many studies reported no association. There were more reports of a positive (rather than negative) association between shorter diagnostic/time to treatment interval and improved outcomes for breast, colorectal, head and neck, testicular cancer and melanoma. A similar pattern, although based on a smaller number of findings, was identified for pancreatic, prostate and bladder cancer. For other cancers the evidence was equivocal or insufficient in quantity. The authors note being unable to assess for publication bias.

Table 1: summary of findings of Neal et al systematic review

	Number of findings: (*2010-2013 only)		
Cancer type	Shorter intervals associated with improved outcomes	No association	Shorter intervals associated with less favourable outcomes
Breast *	5	9	Nil
Colorectal *	7	14	1
Head and Neck	20	21	Nil
Testicular	14	10	Nil
Melanoma	8	9	Nil
Pancreatic	2	3	Nil
Prostate	2	6	Nil
Bladder	3	5	Nil
Lung	5	13	7
Gastric	Nil	9	3
Oesophageal	1	2	1
Cervical	1	3	Nil
Endometrial	4	3	2
Ovarian	1	7	1
Non-melanoma skin	2	1	Nil
Leukaemia	Nil	3	Nil
Lymphoma	Nil	3	2
Myeloma	3	Nil	Nil
Connective tissue	3	3	Nil

Although there was only moderate consensus (even within specific cancer types) as to the nature of associations between time intervals and clinical outcomes the authors conclusion was that, although benefits vary between cancers, it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefit for patients in terms of earlier-stage diagnosis, improved survival and improved quality of life.

Literature searches for systematic reviews and other secondary evidence published since the Neal et al 2013 search cut-off identified seven articles relating to the following:

- Time to chemotherapy (selected cancers)[1]
- Head and neck cancers [9, 10]
- Colon/colorectal cancers[2, 11, 12]
- Prostate cancer[13]

As with the Neal et al review, more recent systematic reviews brought together studies from across countries with different healthcare systems. The potential impact of this heterogeneity is unclear and whether findings from one country are applicable in another - given social factors influencing access to healthcare, such as rurality and insurance status - were discussed in some of the reports.

Time to chemotherapy (selected cancers)

A systematic review published in 2016 examined the evidence on the effect of time to initiation of systemic chemotherapy on survival outcomes in six priority cancers (breast, colorectal, lung, ovarian, myeloma and lymphoma) [1]. Separate literature searches were conducted for each cancer type in April 2014 and study quality was assessed using the Newcastle Ottawa Scale. The work informed Australian guidelines providing cancer-specific recommendations for timely initiation of chemotherapy[3].

For breast cancer all of the identified studies focused on the time interval from surgery to adjuvant chemotherapy rather than chemotherapy as a first treatment. As such, this part of the review is not relevant to the question for this Evidence Synthesis. The same situation applied to studies on ovarian cancer.

Similarly, for colorectal cancers, no studies were identified in the neoadjuvant setting. For asymptomatic metastatic colorectal cancer, the review identified a meta-analysis of two randomised controlled trials (n=84) which found no evidence of a survival benefit for immediate (one month) compared with delayed (until specific symptoms developed, 4-6 months) chemotherapy hazard ratio (HR) for death = 1.15 (95% CI 0.77 to 1.72).

Three retrospective studies were identified relating to small cell lung cancer. None reported an association between increased time to chemotherapy and negative patient outcomes. Definitions of time intervals was different in each study. One of the studies examined time

from first consultation with any doctor to chemotherapy and found that when intervals of <42 days were compared with intervals >42 days, those who had shorter waits had poorer outcome; HR for death= 1.20, p=0.002. This is likely to reflect the urgent treatment of patients with significant symptoms resulting from aggressive tumour biology.

For non-small cell lung cancer five studies examined effect of time intervals to chemotherapy in the setting of inoperable cancer. The studies included other treatment modalities such as combined chemo and radiotherapy. Three of the studies were had been included in the Neal review. None of the studies found an association between time to chemotherapy and survival when examining intervals from 30 days to 6 months. The clinical applicability of this finding was judged to be at risk of bias due to the mixed treatment setting and the retrospective nature of the studies. Guidelines for this patient group, i.e. to avoid delays greater than three weeks, were based on two prospective imaging studies which demonstrated significant tumour growth whilst awaiting treatment.

No relevant studies were identified for myeloma.

For lymphoma, three retrospective cohort studies were identified for potentially curable lymphomas with non-urgent presentation. The first study (n=278) was conducted in patients with diffuse large B-cell lymphoma (DLBCL) and found that intervals from haematology consultation to initiation of chemotherapy of longer than four weeks were not associated with reduced overall survival when compared with intervals of <1 week or 1-4 weeks. The small sample size was noted to compromise the ability of the study to inform practice. A larger study (n=689) in DLBCL reported that time from diagnosis to initiation of chemotherapy of greater than eight weeks was associated with worse overall mortality (HR= 1.20 95%CI 1.03 to 1.41, p=0.020) when compared with less than eight weeks in multivariate analysis. A third study, undertaken in patients with Hodgkin lymphoma (n=879) reported that intervals of over eight weeks between diagnosis and initiation of curative chemotherapy significantly reduced 5-year survival when compared with initiation within 2 weeks (84% versus 90%, p=0.012). For comparisons between <2 weeks with 3-4 weeks and 5-8 weeks there was no survival difference observed. Based on these studies the guideline recommendation was that systemic chemotherapy should commence as soon as possible and within no longer than 4 weeks of the ‘ready for care’ date.

No studies were identified in highly aggressive lymphomas such a lymphoblastic lymphoma.

Head and neck cancers

A systematic review published in 2019 examined the association between time from diagnosis to treatment initiation (DTI) and survival for patients with head and neck cancers. Studies encompassing any or all cancer sub-sites were included e.g. oral cavity, larynx, pharynx, hypopharynx, salivary apparatus[9]. Thirteen articles published between January 2007 and February 2018 were included. Most studies were published from 2016 onwards and only one article overlapped with the Neal et al systematic review. Most studies (10/13) used population-based cancer registry data, so sample sizes were large with several having over 10,000 patients. Study quality was assessed using the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies. Higher scores indicate higher quality with maximum score being 20. Studies ranged in quality score from 10-13 and most studies adjusted for confounders such as stage and sub-site. Meta-analyses were not conducted due to the heterogeneity in reporting of time to treatment thresholds.

The majority of studies examined the effect of prolongation of the DTI interval compared with a referent time frame. In several cases this was 30 days. There was heterogeneity in the definitions of delay e.g. >30 days, >45 days, >120 days and also the width of the time categories. Findings from the two largest primary studies in the systematic review are outlined in table 2. An association between delays in DTI and poorer survival was reported in nine of the 13 studies. The effect size generally increased with longer DTI intervals.

Table 2: findings of the two largest primary studies in head and neck cancer systematic review

Diagnosis to treatment interval category	Adjusted HR death	95% Confidence interval
Primary study 1 (n=51,655) USA 2016		
≤30 days (reference)	1.00	
31-60 days	0.99	(0.96 to 1.02)
61-90 days	1.08	(1.03 to 1.13)
≥91 days	1.23	(1.15 to 1.32)
Primary study 2 (n=21,263) Taiwan 2017		
<30 days (reference)	1.00	
31-120 day	1.18	(1.11 to 1.25)
≥120 days	1.32	(1.19 to 1.47)

A systematic review focused specifically on symptomatic oral cancer and examined the effects of diagnostic delay on cancer disease stage or survival[10]. The literature search was conducted in March 2014.

Ten small studies were identified (total n=1,083), and the Aarhus Statement checklist was used to assess the methodological quality of the individual studies. The studies were published between 1998 and 2012, which means that the review overlaps with the Neal et al systematic review. Five of the ten were studies were included in the Neal et al systematic review.

Delays were variously defined across the studies and included patient delays, professional delays, referral delays and combinations thereof. Durations of delays were frequently characterised as >30 days but in some cases were longer e.g. >45 days, > 3 months.

Meta-analyses with pre-determined subgroup analyses were conducted. Findings are presented in table 3. There were only a small number of studies for each analysis. In all but one analysis there was a statistically significant increase in risk of mortality/more advanced cancer stage at diagnosis associated with delay.

Table 3: Meta-analysis of studies exploring the association between delay to diagnosis and outcomes for oral cancer

Association of:	Number of studies	Pooled Odds Ratio for mortality (OR)	Heterogeneity (Ri)*
Mortality and any delay	4	1.35 (95% CI 0.84 to 2.18)	0.94
Mortality and referral delay	2	2.48 (95% CI 1.39 to 4.42)	0.00
Cancer stage and any delay	7	1.66 (95% CI 1.25 to 2.20)	0.49
Cancer stage and any delay – high quality studies (score >10/20 items)	2	2.44 (95% CI 1.36 to 4.36)	0.00
Cancer stage and professional delay	3	2.15 (95% CI 1.08 to 4.29)	0.74
*Proportion of total variance due to between-study variance (0.00=no heterogeneity between studies, 0.94=large heterogeneity between studies)			

Colon cancer

A systematic review focused on the effect of time from diagnosis to initiation of surgical treatment on outcomes for patients diagnosed with colon cancer. A literature search to June 2017 identified five observational studies[2]. Only one of the studies was included in the Neal et al review which had combined colon and rectal cancer into one disease category. Study size ranged from 458 to 7,989. Settings were Denmark, Canada, America and South Korea. Outcomes in the studies included disease/cancer specific survival, overall survival at varying follow up durations, and five year survival.

The risk of bias of the studies was assessed using the Downs and Black checklist for measuring study quality. Two of the studies scored less than 20 (out of a possible 28 points) due to deficiencies in reporting and adjustment for potential confounders.

No meta-analyses were undertaken due to heterogeneity in time intervals examined across the studies, and the way in which comparison groups were specified. At the extremes, delay categories encompassed intervals from 1-14 days to 58-249 days.

Four of the five included studies reported no association between treatment delay and reduced overall survival for patients with colon cancer. The remaining study compared time from diagnosis to surgery of 1-14 days versus >43 days and reported HR =1.2 for overall survival (95% CI 1.1 to 1.3, p= 0.013). For the same time interval comparison in this study there was no association with disease specific survival HR=1.0 (95% CI 0.8 to 1.1, p=0.63).

Colorectal cancer

A pooled analysis of seven independent data sets from population-based studies (total n=11,720) examined the relationship between stage of colorectal cancer (CRC) at diagnosis and the primary care and secondary care components of the total diagnostic interval (time from first presentation of symptoms to diagnosis)[11]. It is unclear how the datasets were identified, but all of the data were drawn from publicly funded universal healthcare systems and six of the seven data sets were published. Scottish Cancer Registry data from 1997/8 was included. Only patients with recorded symptoms of CRC or CRC-related visits in the year before diagnosis were included; screen detected cases and cases with emergency presentation outwith primary care were excluded. The primary outcome was stage of CRC defined within local cancer registry.

Each data set was analysed separately then combined for individual patient data (IPD) analysis with data adjusted for age, gender and the presence of cancer alarm symptoms.

Reflecting the waiting time paradox, combined IPD analysis for total diagnostic interval found decreasing odds of advanced CRC associated with longer intervals ($p<0.001$). This pattern was not statistically significant for the individual cohorts.

When the primary and secondary care components were analysed separately, a more complex waiting times paradox emerged suggesting inherent difference in the prognosis of patients given different medical priority in primary versus secondary care:

- There was a statistically significant (p=0.004) ∩-shaped association with increasing (peak at around 90 days) and subsequently decreasing (from 90 to 365 days) odds of advanced CRC stage with longer primary care interval (date of first presentation to date of referral). Adjusted odds of being diagnosed with an advanced stage tumour were around 8% (95% CI 2% to 12%) higher for patients who waited 90 days for referral compared with 30 days.
- For the secondary care interval there was a statistically significant (p<0.001) U-shaped association with decreasing (trough at around 60 days) and subsequently increasing (from 60 to 365 days) odds of advanced CRC with longer secondary care intervals. Adjusted odds of being diagnosed with an advanced stage tumour were around 15% (95% CI 12% to 20%) lower for patients who waited 60 days from referral to diagnosis compared with 30 days.

There was no comment in the study about the differences between colon (69% of patients) and rectal (31% of patients) cancers.

A Cochrane systematic review compared immediate versus delayed chemotherapy for patients with asymptomatic, incurable, metastatic colorectal cancer[12]. This population group makes up approximately 20% of newly diagnosed patients. Three RCTs (n=351) were included in the meta-analysis which reported an overall survival HR = 1.17 (95%CI 0.93 to 1.46) for the comparison of immediate versus delayed chemotherapy. The authors concluded that timing of chemotherapy may make little or no difference to overall survival. This is closely in line with the review of delays to chemotherapy discussed earlier in this Evidence Synthesis which was based on two of the three studies identified in this Cochrane review[1]. The quality of the evidence was assessed as low because of concerns regarding imprecision due to small patient numbers. Two of the studies in the review reported on quality of life. There was no clear difference between study arms.

Prostate cancer

A systematic review examined whether delay from diagnosis to initiating active curative therapy in prostate cancer results in poorer pathological, biochemical and mortality outcomes[13]. Seventeen relevant studies were identified. The review time frame with literature search to September 2012 overlapped with the Neal et al work but, since it encompassed cancers identified through screening a greater number of studies were identified.

Treatment delay was variously defined across the included studies. In four studies this was specified according to deviation from the median interval (which ranged from 56 days to 3.7

months). Other studies used standard intervals such as 3 months, 6 months or 60 days as the reference interval and compared this with outcomes of longer or shorter intervals. In eleven of the 17 studies it was unclear whether the delay was intended, for example as part of an active surveillance/ watchful waiting strategy - or unintended.

Outcome variables included biochemical recurrence (BCR) rates after treatment with curative intent (15 studies), pathological characteristics after radical prostatectomy (8 studies), overall or cancer specific survival (3 studies) and metastatic disease (2 studies).

All of the studies were retrospective and although no formal appraisal of methodological quality was provided the review authors noted that all were limited in varying degrees by suboptimal study design.

The authors categorised studies into four groups according to their findings:

1. Seven studies found no impact of treatment delay on oncologic outcomes. Two of these included only men with low risk disease while the other five included men with higher risk prostate cancer.
2. Four studies indicated an association between treatment delay and poorer outcomes but this was lost when multivariate analysis included factors such as age, prostate specific antigen (PSA) density, cancer stage and grade.
3. Two studies identified protective effect of delay to treatment initiation. This was considered likely to be due to confounding by indication where tumours with more favourable characteristics are both treated later and have better outcomes.
4. Four studies found that treatment delay (>9 months, 19.2 months, >2.5 months, >6 months) was associated with poorer outcomes in terms of BCR rates, higher Gleason scores, positive surgical margins, frequency of disease upgrading and prostate specific antigen (PSA) progression free survival. None found a relationship between delays and distant metastases or overall survival. In two of the studies the finding applied to intermediate risk and to high risk groups but not to low risk patients. The other two studies included only low risk patients but their risk may have been misclassified by initial biopsy leading to selection bias.

From a descriptive review of the evidence base the authors concluded that for men with low risk prostate cancer a treatment delay of several months or even years does not appear to compromise long-term oncologic results following definitive treatment.

Whilst the overall conclusion of the systematic review reflects the finding that the majority of studies did not find an association between the variously defined treatment delays and outcomes the conclusion is limited by the several aspects of the literature:

- Only a few studies included patients with intermediate or high risk disease.

- Most studies did not provide information on reasons for treatment delay and what the thresholds were for active surveillance versus treatment initiation.
- The effect of comorbidity on decisions to initiate treatment may introduce bias to findings.

Ongoing systematic reviews

Three ongoing systematic reviews were identified, one published as a meeting abstract:

- Association between time to treatment and survival in non-small cell lung cancer: a systematic review (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=99239)
- Delays in diagnosis of primary central nervous system tumours in adults: a systematic review (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=51602)
- A systematic review and meta-analysis of delaying radical cystectomy and the effect on survival in bladder cancer patients

  (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=118936)

  https://www.frontiersin.org/Community/AbstractDetails.aspx?ABS_DOI=10.3389/conf.fonc.2019.01.00007&eid=6817&sname=Bladder_Cancer_Translational_Research_Meeting

Patient and social aspects

A systematic review with a limited literature search (PubMed only) to August 2013 synthesised quantitative survey data on adult cancer patients' preferences or priorities around hospital care[14]. Eleven patient survey studies were included representing The Netherlands, US, Canada, UK and Sweden. Survey items relating to 'rapid diagnosis and treatment' were examined in six of the 11 studies, and this theme emerged from the data synthesis as one of the most important dimensions of care for patients alongside high professional standards and information about treatments. Several sources of bias and limitations around the data were highlighted:

- Patients were primarily those who had specialist treatment with curative intent and survey response rates ranged from 12.5% to 77%.
- Although some care dimensions were rated as more important than others, patients generally rated every care item to be important.
- There was large variation in the 592 items explored across the studies. Perception of the meaning of items may vary greatly across the different study contexts. Although

items encompassed within the ‘rapid diagnosis and treatment’ dimension scored high in the synthesis, the ‘waiting time’ dimension was a lower priority.

Conclusion

Based on the published secondary literature it is not possible to reach robust conclusions on the association between cancer outcomes and time intervals to diagnosis and treatment. This is due to lack of standardisation around how time intervals are specified and compared, the range of outcomes examined and the presence of confounding by indication that characterises the research evidence.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence syntheses has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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