Scottish Intercollegiate Guidelines Network (SIGN)

Long-term follow up of survivors of childhood cancer

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Overview of talk

Overview of Scottish Intercollegiate Guideline Network (SIGN) methodology

Challenges this level of rigor imposes considering the lack of high level evidence for many of the pediatric outcomes

Examples of some clinical recommendations in SIGN 132

Scottish Intercollegiate Guidelines Network (SIGN)

Formed in 1993

- Objective:
- Improve the quality of health care for patients in Scotland (and elsewhere)
- Reduce variation in practice – through the development and dissemination of clinical guidelines based on a systematic review of the current scientific evidence
- Neither Cookbook nor Textbook
- Not “expert opinion”
- Importantly do not do a cost effective analysis around any recommendations (cf NICE)

(Appraisal of Guidelines for Research and Evaluation in Europe)

ll relevant disciplines included in guideline development group - multidisciplinary

learly described objectives / questions

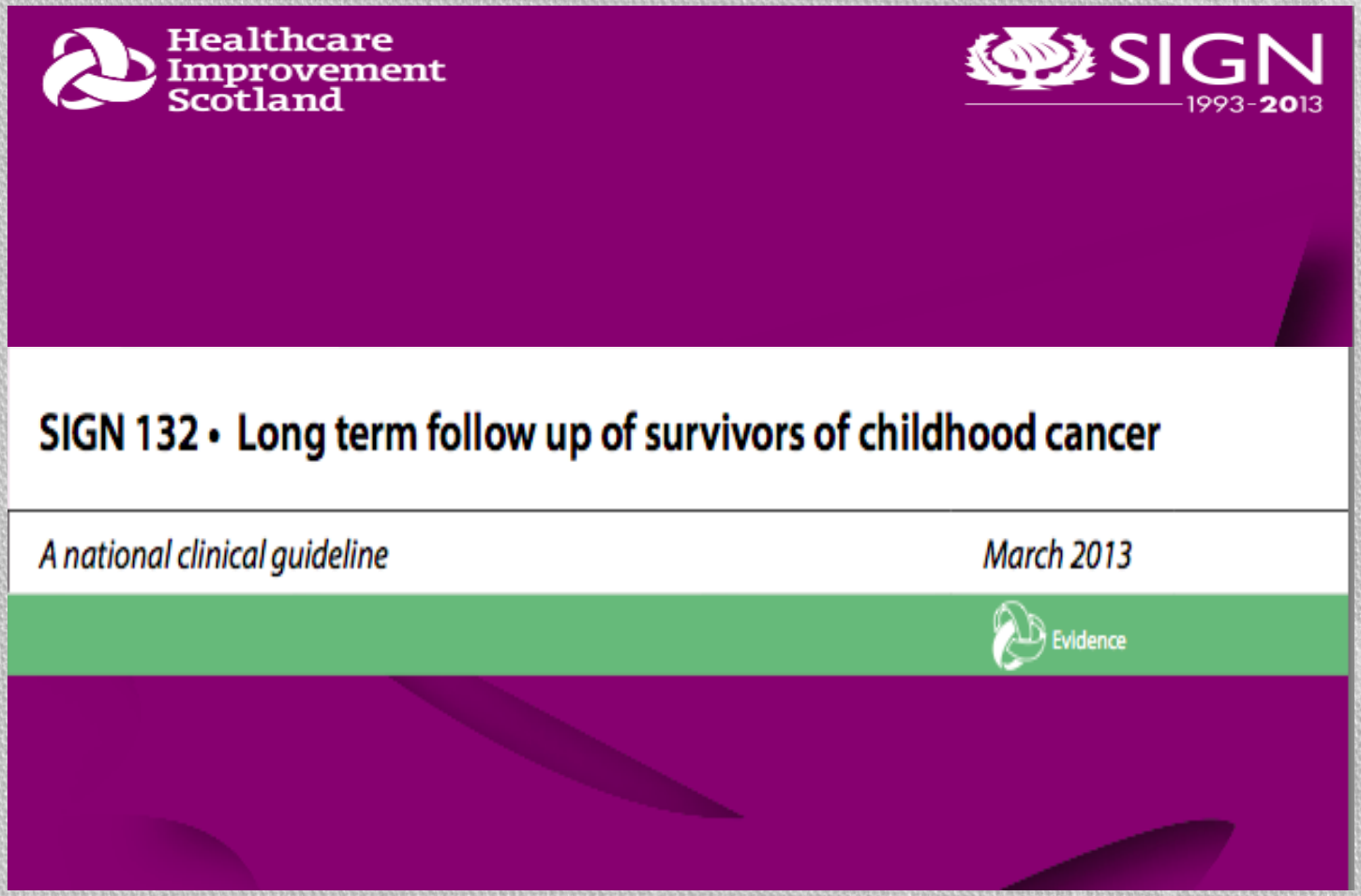
atient involvement

ystematic methods used to search for evidence

ecommendations clearly linked to evidence

uideline has undergone external review prior to publication

SIGN 132 updates SIGN 76 (2004)



Wallace, W.H.B., Thompson, L. & Anderson, R.A., 2013. Long term follow-up of survivors of childhood cancer: summary of updated SIGN guidance. BMJ (Clinical research ed.), 346, p.f1190.

SIGN Topic Selection

- Wide variation in practice or outcomes –clinical uncertainty
- Proven effective treatment to reduce mortality and morbidity
- Iatrogenic diseases or risky interventions
- Clinical priority areas (Cancer & Children)
- A body of evidence available for critical appraisal
- Perceived need for the guideline from stakeholders

The Guideline Development Group: SIGN 132

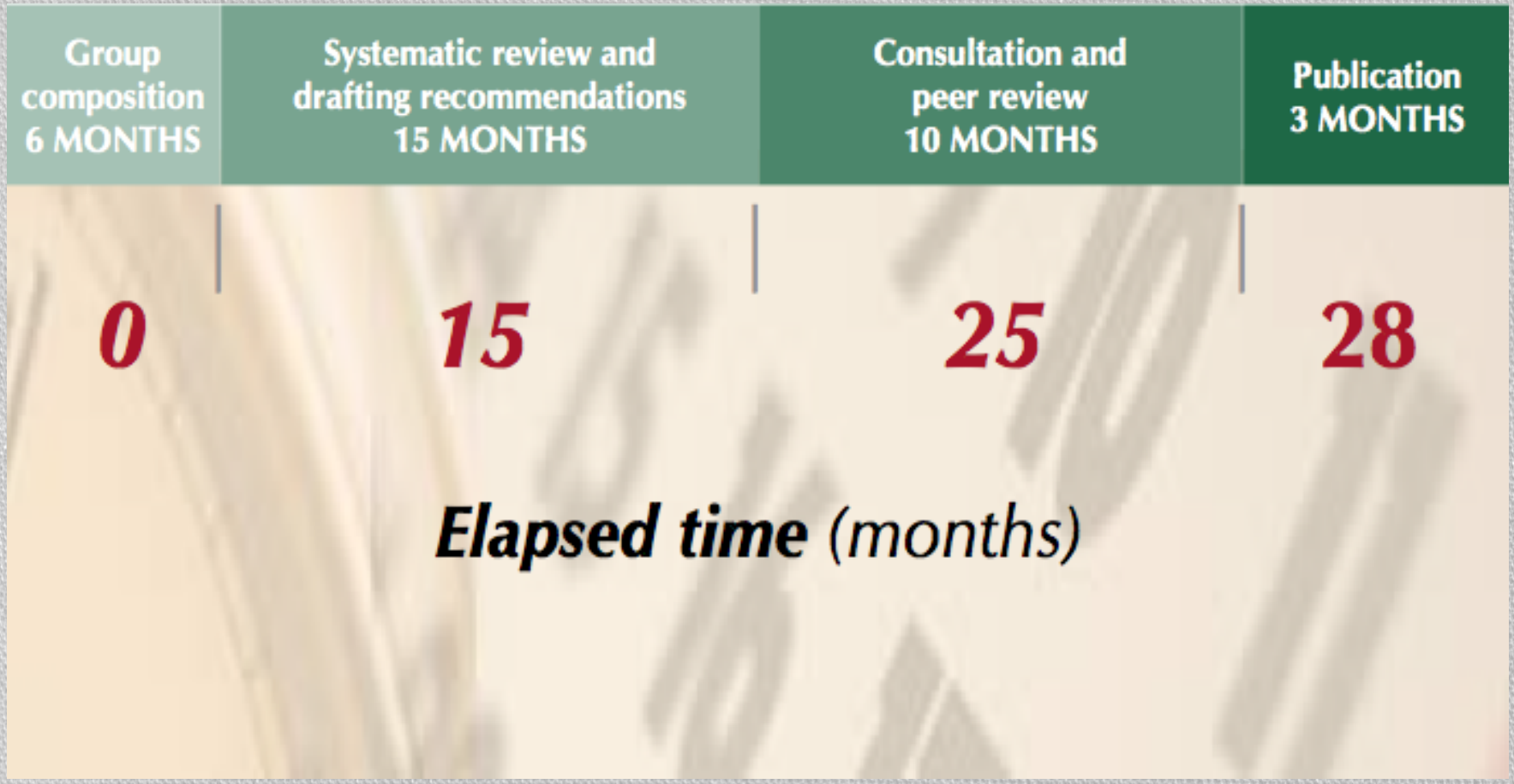
THE GUIDELINE DEVELOPMENT GROUP

Professor W Hamish Wallace *(Chair)*	*Consultant Paediatric Oncologist, Royal Hospital for Sick Children, Edinburgh*
Professor Richard Anderson *(Vice-Chair)*	*Professor of Clinical Reproductive Science, University of Edinburgh*
Ms Juliet Brown	*Evidence and Information Scientist, SIGN*
Dr Susan Buck	*General Practitioner, Edinburgh*

Multidisciplinary
Patient Involvement
No financial inducements (expenses)
Everyone completed a conflict of interest statement

	Glasgow
Miss Jen Layden	*Programme Manager, SIGN*
Mrs Caroline McManus	*Childhood cancer survivor, Edinburgh*
Dr John Murphy	*Consultant Haematologist, Monklands Hospital, Airdrie*
Dr Dzung Nguyen	*Consultant Paediatrician, St John's Hospital, Livingston*
Dr Stephen Rogers	*Consultant Haematologist, Victoria Hospital, Kirkcaldy*
Dr Guftar Shaikh	*Paediatric Endocrinologist, Royal Hospital for Sick Children, Glasgow*
Ms Ailsa Stein	*Programme Manager, SIGN*
Dr Lorna Thompson	*Programme Manager, SIGN*

The SIGN Guideline Process



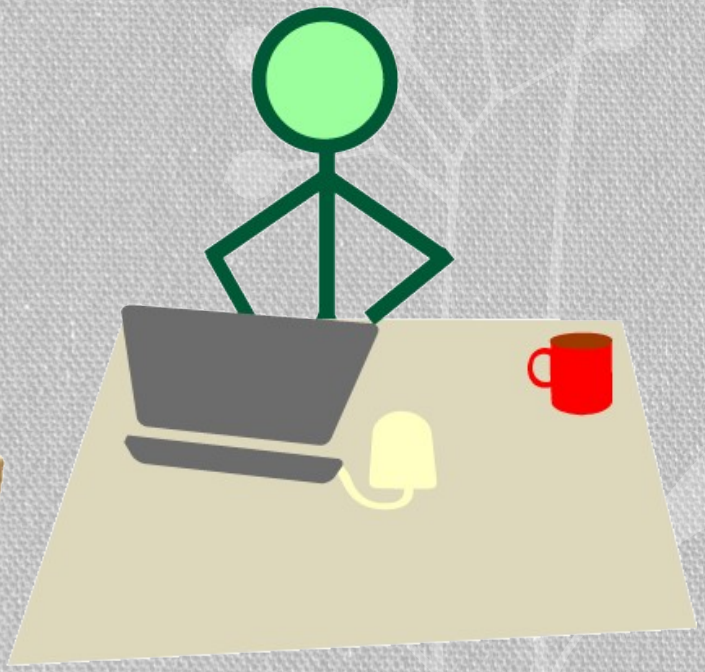
Timetable for guideline development

Months 1-3	▪ Define remit of guideline ▪ Attend critical appraisal training ▪ Plan development process ▪ Share relevant knowledge and experience ▪ Identify key questions/terms for literature search (with advice from SIGN Information Officer ▪ Discuss requirements of systematic literature review	***Prepare group and finalise remit:*** **3 months**

Key questions identified

Key question
1. What are the risks of specific treatment modalities for primary cancers in the development of a subsequent primary cancer?
2. What surveillance strategies (frequency, modality and intervals) exist for monitoring or detecting secondary malignancies? Should certain monitoring strategies be avoided?
3. Are childhood cancer survivors at increased risk of developing metabolic syndrome? (Consider: type II diabetes, obesity, insulin resistance, hyperlipidaemia and hypertension)
4. What are the effects of treatment for childhood cancer on skeletal/bone development? (Consider: fracture, osteoporosis, avascular necrosis, bone mineral density, rickets)
5. What are the effects of treatment for childhood cancer on cardiac outcomes? (Consider: cardiac failure, mortality, cardiac transplantation, coronary heart disease, hyperlipidemia, iron overload, arrhythmias)
6. Are any cancer survivor subgroups at higher risk of developing cardiac problems following treatment?
7. Which diagnostic tests/interventions are appropriate for detecting cardiac failure, coronary heart disease and hyperlipidemia in survivors of childhood cancer?
8. What is the risk to fertility of treatment for childhood cancer? (Consider: infertility, pregnancy outcome (late and early), hormone deficiency, sexual dysfunction, early menopause)
9. Can early menopause be predicted?
10. How can future fertility of males and females with childhood cancer be protected?
11. Do adult survivors of childhood cancer remain infertile and how often should fertility be assessed?
12. What is the risk of congenital abnormalities in offspring of survivors of childhood cancer?

Literature searches



Guidelines

Review + Recommendations

Critical appraisal of the evidence

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Grades of Recommendation:
Linked to strength of the evidence

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

From Evidence to Recommendations

- he grading of the recommendation (A, B, C or D) does **Not** relate to the importance of the recommendation - but to the strength of the supporting evidence.
- aturally problematic as it is assumed that a B or C level recommendation is more important than a D recommendation – this is not the case.
- erhaps a traffic light system would be more explicit and helpful?

Traffic Lights

top –Don’t do it..

ot sure –More Research required

es, Go do it..

Timetable for guideline development

Months 1-10	▪ Review abstracts to select papers for detailed review ▪ Clarify criteria used to select or reject papers ▪ Detailed literature review, grading and synthesis of evidence (often undertaken in subgroups)	***Literature search and appraisal:*** ***10 months***

Timetable for guideline development

Months 11-15	▪ Draft recommendations derived from evidence review ▪ Draft guideline prepared ▪ National open meeting held to present and discuss draft recommendation	***Draft guideline: 5 months***

Timetable for guideline development

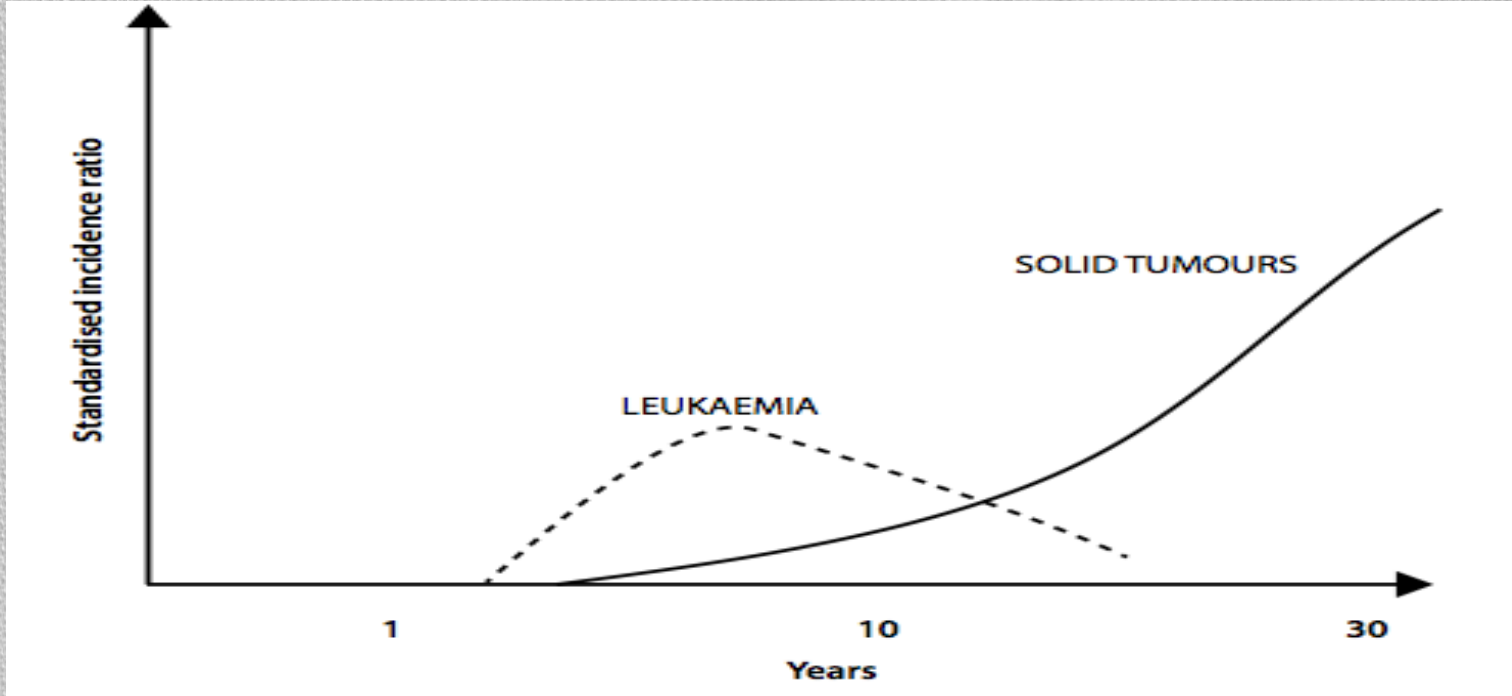
Months 16-25	▪ Feedback from national meeting incorporated into draft guideline. Draft is edited by group with assistance from SIGN Executive ▪ Guideline sent for external peer review ▪ Feedback from external reviewers incorporated into draft guideline	***Post national meeting review; Peer review*** ***10 months***
Months 26-28	▪ Review by SIGN Editorial Group ▪ Publication and dissemination	***Final editing***

Problems with reaching recommendations from the Late Effects Evidence base

- Often evidence identified of increased risk of adverse outcome – from prospective cohort studies
- Usually no evidence for effectiveness of intervention – eg screening for that outcome
- Leads to recommendations such as “should be aware of increased risk of…”

Subsequent Primary Cancers

C Healthcare professionals should be aware that all survivors of childhood cancer who were treated with radiotherapy are at risk of subsequent primary cancer and should adopt a high index of suspicion when assessing health concerns.



Subsequent Primary Cancers

CANCER SCREENING AND SURVEILLANCE IN SURVIVORS OF CHILDHOOD CANCER

No studies were identified which explored any benefits or harms of specific screening programmes for survivors of childhood cancer, nor were any studies identified on outcomes for survivors of childhood cancer entering national screening programmes at an earlier age than for general population groups.

Cardiac Effects

C	**Survivors of childhood cancer who received either anthracyclines or radiation to a field that included the heart should be assessed with respect to cardiac muscle function.**
D	**Healthcare professionals should reassure survivors of childhood cancer who did not receive anthracyclines or radiation to a field that included the heart that the lifelong risk of treatment-related cardiac problems is very low.**

Treatment of cardiac problems

There is limited evidence on the efficacy of ACE inhibitors for the treatment of anthracycline-induced cardiomyopathy in childhood cancer survivors

✓ Patients who develop heart failure should be treated according to evidence based guidelines for heart failure therapy.

Fertility preservation (Males and Females)

D	**Teenage boys should be referred for semen cryopreservation if their fertility is considered to be at risk.**

D	**Cryopreservation of ovarian tissue** (within the context of a clinical trial) **should be considered in girls at high risk of premature ovarian insufficiency.**

Risk of congenital abnormalities in offspring of survivors of childhood cancer treatment

wo Danish population based cohort study rated 2+

- Winther JF et al. JCO 2012;30(1):27-33
- Winther JF et al. Clin Genet 2009;75(1):50-6

C	**Healthcare professionals should provide reassurance to survivors of childhood cancer that their offspring are not at increased risk of congenital abnormality.**

SIGN

Implementation

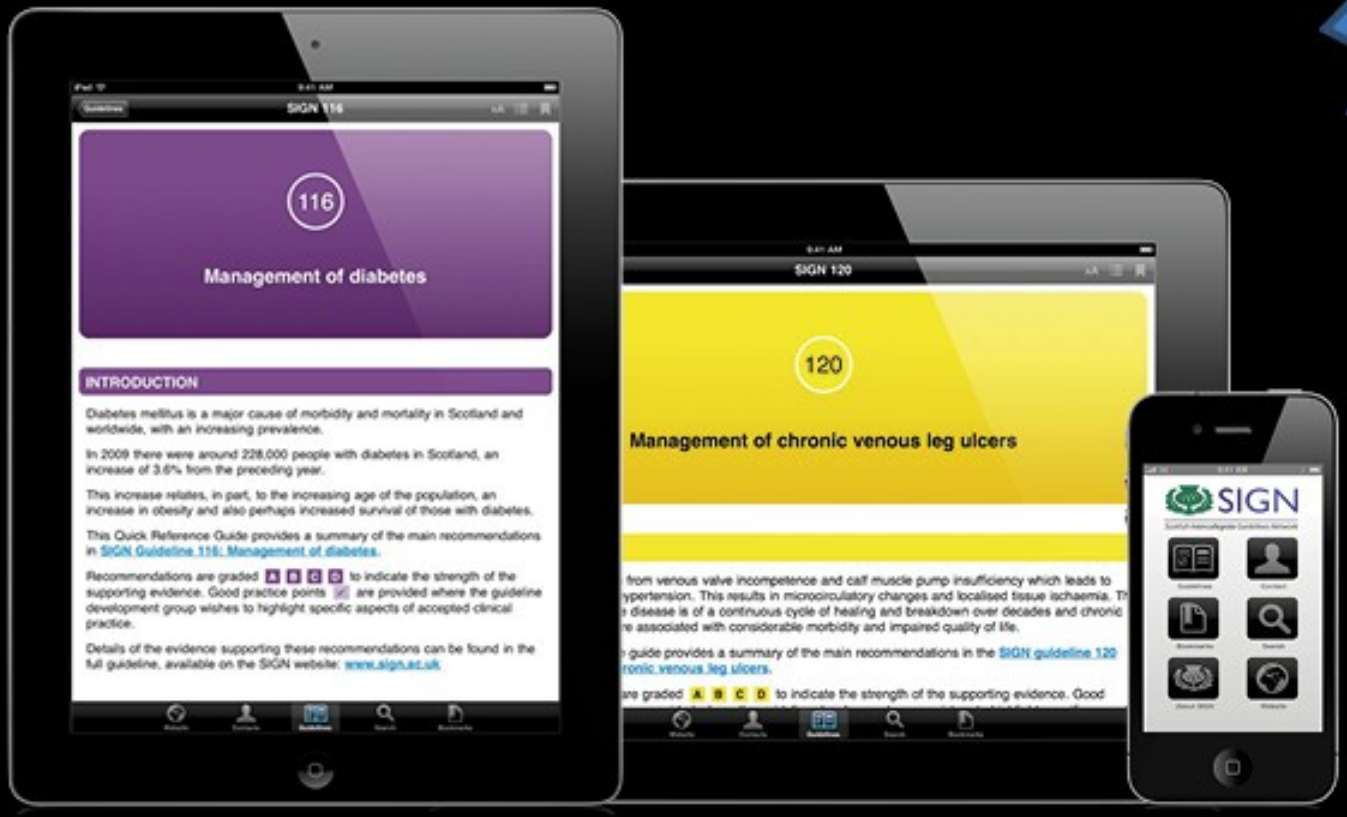
SIGN Implementation strategy

- Dissemination throughout each NHS Heath Board in Scotland
- Facilitated by the MSN for Children and Young People with cancer in Scotland
- Audit tool needs to de designed and key points to audit highlighted
- Involvement of patient groups
- Investment in nurse led and medically supervised long-term follow up
- Internet applications (Apps)

Healthcare Improvement Scotland

SIGN
Scottish Intercollegiate Guidelines Network

The award-winning ★★★★★ SIGN guideline app



eHealth AWARD WINNER 2011

Best NHS Scotland use of Mobile technology in NHS Scotland

★★★★★ *An invaluable tool for medics, nurses, other healthcare professionals, and patients! Excellent!*

SIGN 132 on my iphone

Long term follow up of survivors of childhood cancer

INTRODUCTION

This Quick Reference Guide provides a summary of the main recommendations in SIGN 132 Long term follow up of survivors of childhood cancer.

Recommendations are graded A B C D to indicate the strength of the supporting evidence. Good practice points ✓ are provided where the guideline development group wishes to highlight specific aspects of accepted clinical practice.

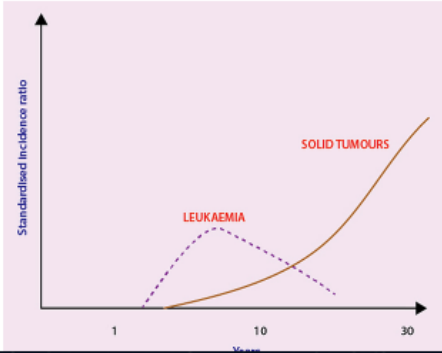
Details of the evidence supporting these recommendations can be found in the full guideline, available on the SIGN website: www.sign.ac.uk

SUBSEQUENT PRIMARY CANCERS

Increased risk

C Healthcare professionals should be aware that survivors of childhood cancer are at par ticular and lifelong increased risk of developing a subsequent primary cancer and that this may occur at any site on the body.

Schematic representation of the onset and duration of risk for subsequent leukaemias and solid tumours up to 30 years following treatment for childhood cancer.



SIGN app: International uptake

1st 2011 - April 1st 2013

279

- Downloads April
- **81,**
- Top 10 by country

1. UK
2. USA
3. Australia
4. Canada
5. Ireland
6. Malaysia
7. Kuwait
8. Spain
9. Hong Kong
10. Thailand

Summary (SIGN 132)

- Rigorous methodology, time consuming, multidisciplinary (including patients) & has some limitations when the strength of the evidence base is weak
- Level of Recommendations are linked to the strength of the evidence, not the importance of the recommendation
- Limited value as a clinical tool because of lack of evidence for interventions
- Highlight areas for future research
- Implementation is difficult – development of App is a positive step
- No cost effective analysis

Acknowledgements

SIGN 132

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Thank You

ESLCCC 2014
15-16 September 2014 Edinburgh, Scotland

Save the date and join us **15 – 16 September 2014** in the historic city of **Edinburgh** UK