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Original Article

The Three-item ALERT-B Questionnaire Provides a Validated Screening Tool to Detect Chronic Gastrointestinal Symptoms after Pelvic Radiotherapy in Cancer Survivors

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Abstract

Aims: Although pelvic radiotherapy is an effective treatment for various malignancies, around half of patients develop significant gastrointestinal problems. These symptoms often remain undetected, despite the existence of effective treatments. This study developed and refined a simple screening tool to detect common gastrointestinal symptoms in outpatient clinics. These symptoms have a significant effect on quality of life. This tool will increase detection rates and so enable access to specialist gastroenterologists, which will in turn lead to improved symptom control and quality of life after treatment.

Materials and methods: A literature review and expert consensus meeting identified four items for the ALERT-B (Assessment of Late Effects of RadioTherapy - Bowel) screening tool. ALERT-B was face tested for its usability and acceptability using cognitive interviews with 12 patients experiencing late gastrointestinal symptoms after pelvic radiotherapy. Thematic analysis and probe category were used to analyse interview transcripts. Interview data were presented to a group of experts to agree on the final content and format of the tool. ALERT-B was assessed for reliability and tested for validity against the Gastrointestinal Symptom Rating Scale in a clinical study (EAGLE).

Results: Overall, the tool was found to be acceptable in terms of wording, response format and completion time. Participant-reported experiences, including lifestyle modifications and the psychological effect of the symptoms, led to further modifications of the tool. The refined tool includes three questions covering rectal bleeding, incontinence, nocturnal bowel movements and impact on quality of life, including mood, relationships and socialising. ALERT-B was successfully validated against the Gastrointestinal Symptom Rating Scale in the EAGLE study with the tool shown broadly to be internally consistent (Cronbach's $\alpha = 0.61$ and all item-subscale correlation [Spearman] coefficients are > 0.6).

Conclusion: The ALERT-B screening tool can be used in clinical practice to improve post-treatment supportive care by triggering the clinical assessment of patients suitable for referral to a gastroenterologist.

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Key words: Cancer; quality of life; radiotherapy

Introduction

Pelvic radiotherapy is an effective treatment for a range of malignancies, including those affecting the gynaecological (uterus, cervix, vagina and vulva), urological (prostate and bladder) and gastrointestinal (rectum and anus) tracts [1]. Although efficacious, it is recognised that pelvic radiation can lead to gastrointestinal, urological and psycho-sexual symptoms in the months or years after

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treatment [2]. However, these symptoms are often under-treated, with no simple tool available to easily identify patients [3]. Here we report on the development of a simple screening tool, ALERT-B (Assessment of Late Effects of RadioTherapy - Bowel), to be used in oncology clinics to identify patients with ongoing gastrointestinal symptoms after pelvic radiation for cancer.

In excess of 20 abdominal symptoms have been described after pelvic radiotherapy, including diarrhoea, rectal bleeding, abdominal pain, and faecal incontinence [3,4]. Each symptom can have many causes and patients often report several symptoms [3]. Bowel symptoms can be related to treatment dose of radiotherapy, cancer type, cancer stage, length of time since treatment or conversely it can be unrelated to radiotherapy [5].

Acute symptoms caused by inflammation and mucosal damage tend to begin around the second week of treatment and often settle within 3 months [6]. Symptoms that persist or appear after this time frame as a consequence of ischaemia and fibrosis are considered to be late or chronic effects [6]. Studies have suggested that around 90% of patients have a change in bowel function, of which up to 40% describe these symptoms to be moderate or severe with an impact on quality of life [3,7]. The incidence of these symptoms is increasing with improved cancer survivorship and increased availability of radiotherapy [8]. These symptoms affect various aspects of patients' lives, including physical, psychological and social functioning [7].

Although cellular pathological changes induced by radiotherapy cannot be reversed, identified gastrointestinal symptoms can be treated by correcting the functional physiological changes induced by radiotherapy [3,9]. Gastroenterology healthcare professionals can systematically investigate these symptoms and suggest medical, dietary or endoscopic interventions that can help to alleviate these distressing complaints [2,10].

Chronic radiation-induced late effects, caused by vascular damage, are substantially more common than healthcare professionals generally recognise [3], and are under-reported by patients [3]. There are several possible reasons for this. Patients may be too embarrassed to mention their symptoms or feel that they are an inevitable consequence of their treatment or age [7]. Patients may also believe that there are other more important issues to discuss during time-limited consultations [6]. A number of clinicians may also believe that few treatment options are available for these patients, thus identification of gastrointestinal symptoms will have limited clinical benefit [6]. Consequently, gastrointestinal symptoms may not be routinely enquired about and if reported may not be linked with previous radiotherapy [11].

For a screening tool to be effective in a busy clinical setting, the questionnaire needs to be succinct and straightforward to administer. The Late Effects on Normal Tissue Subjective, Objective, Management, and Analytic (LENT-SOMA) questionnaire (now largely superseded by Common Terminology Criteria for Adverse Events [CTCAE]) [12], was developed to assess a wide range of problems after

radiotherapy. Therefore, despite efforts to reduce the length of this questionnaire (in particular, for prostate cancer patients for the present study) [13], such LENT-SOMA questionnaires (and associated variants) are too long to be used routinely as a screening tool [14]. Other symptom-based scoring systems are also either too lengthy (e.g. the modified Inflammatory Bowel Disease Questionnaire [IBDQ] [15] with 32 items and the Gastrointestinal Symptom Rating Scale [GSRS] [16] with 15 items) or they focus on just one symptom (e.g. the Vaizey Incontinence Questionnaire with seven items focussing on bowel continence) [17]. Therefore, there is a need for a simple screening tool that can be used in clinical practice. Cognitive interviewing has been empirically validated as a technique for pretesting questionnaires and screening tools [18]. It can be used to identify issues pertaining to the content, format and interpretation of questions using a small number of selected participants who provide in-depth information about the screening tool [19,20]. The aims of this study were to design, test and validate a simple screening tool that can effectively detect patients with ongoing gastrointestinal symptoms that have developed after pelvic radiotherapy for cancer.

Materials and Methods

Phase One

The ALERT-B screening tool was developed and validated in four phases (Figure 1). Phases one to three were part of the DESIGNER study (DEveloping a Simple screening tool to detect chronic GastrointestiNal symptoms after pelvic radiothERapy in cancer survivors) and phase four was part of the EAGLE study (Improving the Wellbeing of Men by Evaluating and Addressing the Gastrointestinal Late Effects of Radical Treatment for Prostate Cancer). During phase one, an initial expert consensus day was held in April 2013 to generate the screening tool items. A range of existing questionnaires were reviewed, including the Vaizey Incontinence Questionnaire, LENT-SOMA, GSRS and the modified IBDQ [14–17], for post-radiotherapy patients as well as those that assess gastrointestinal symptoms and quality of life. Andreyev *et al.*'s suggested screening questions were also reviewed during the consensus meeting [2]. A patient representative gave advice on acceptable wording for either self-administration of the tool or with assistance from healthcare professionals.

Phase Two

In phase two, the newly developed ALERT-B screening tool was face tested for its usability and acceptability using cognitive interviewing with a representative patient group. The study aimed to interview around 10–15 participants, based on Willis' recommended sample size [18].

Eligible patients for the cognitive interviews in phase two of the study were identified and approached by healthcare professionals at oncology and gastroenterology

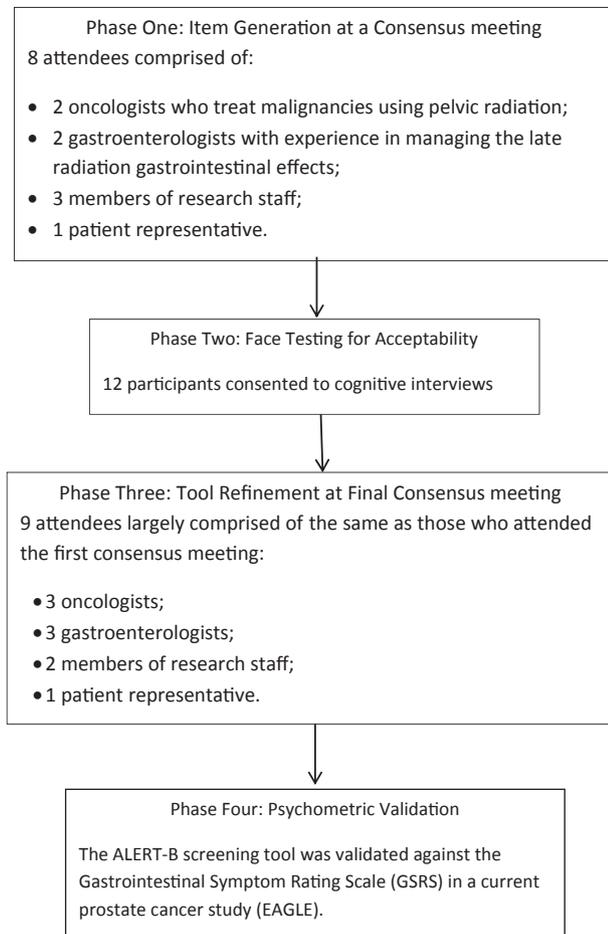


Fig 1. Study profile. The development of the ALERT-B screening tool consists of four phases involving two expert consensus meetings, qualitative interviews with participants who developed late gastrointestinal symptoms after pelvic radiotherapy and a validation phase.

clinics from two hospitals in South Wales. Inclusion criteria included patients 16 years or older, received radical pelvic radiotherapy more than 3 months previously, with no evidence of current malignant disease, experiencing chronic gastrointestinal symptoms since receiving pelvic radiotherapy, able to give informed consent to participate in the study and able to understand and communicate to the extent needed to participate in the interview. Exclusion criteria included evidence of active malignant disease, patients under secondary care review for an active known gastrointestinal disease, any factor that affects communication and comprehension, and age below 16 years.

All eligible participants were given a letter and a participant information sheet until the sample size was met. Participants completed and posted the return slip on the invitation letter to express interest in the study and they were then contacted by the researcher after 24 hours to arrange an interview. Interviews were conducted by one researcher with an academic clinical background, and took place either in the participant's home or a quiet clinic space according to preference. The researcher gained written

informed consent from all participants before the start of the interview. Participants' clinical and demographic information were recorded by the researcher or clinician from the study team.

In line with sample size recommendations [18], 12 patients (six men and six women) were recruited and interviewed by the researcher between October 2013 and January 2014. The final decision to close recruitment was based on the researcher's experience and when no new themes were mentioned by participants. Three of the interviews took place at an outpatient clinic and nine in the participants' homes. All those who were recruited completed the study with no drop outs. This cognitive interview study was approved by the North Wales Research Ethics Committee (REC) (Central & East) Proportionate Review Sub-Committee (reference 13/WA/0243).

The cognitive interviews assessed participants' understanding of instructions and questions in the screening tool, ability to make a judgement about an appropriate response and response format. A concurrent debriefing approach was used with a structured interview guide, developed specifically for this study. This interview guide used preselected probes, designed to fit alongside coding categories to test the screening tool in specific domains. 'Verbal probing' techniques were used when specific elaboration regarding aspects of the question were required [18]. Specific verbal probes were used to address individual difficulties as they arose. Recognised probe categories were used, such as comprehension, paraphrasing and recall to assess issues, such as word comprehension. Before the interview, the researcher observed and timed the participants and noted if participants seemed to struggle with any aspects of the screening tool.

The interviews were digitally recorded and transcribed verbatim, and the transcripts were imported into NVivo 10 (QSR) qualitative analysis software for coding [22]. Thematic analysis was used to analyse the interview transcripts and allowed the researcher to undertake both deductive and inductive analyses [23]. The deductive analysis helped to search for specific items and inductive analysis explored unsolicited comments made by the participants (see [Supplementary Material](#)).

Phase Three

In phase three, a second and final consensus meeting was held in February 2014 to review and refine the tested screening tool based on the findings of phase two. Expert opinion and interview results data were used to review and refine the screening tool in readiness for use in local practice.

Phase Four

In phase four, ALERT-B was psychometrically validated against GSRS in the EAGLE study. The EAGLE study aims to set up and test a new gastroenterology service at three UK sites that will systematically investigate and treat prostate cancer patients who develop late gastrointestinal

symptoms after pelvic radiotherapy. ALERT-B and GSRS were completed by prostate oncology clinics to determine eligibility to the study. GSRS is a disease-specific patient completed instrument of 15 items combined into five scales relating to abdominal pain, reflux, diarrhoea, indigestion and constipation. The reliability and validity of GSRS have previously been tested [16,21]. Recruitment of subjects was initially constrained to cover a 6 month period, with an aim to recruit around 150 participants. This sample size was considered more than sufficient for the purposes of an analysis of validity using Spearman correlation coefficients.

Inclusion criteria for phase four included patients attending oncology clinics who received radiotherapy at least 6 months previously and were aged over 18 years. Exclusion criteria included any factor that affects communication or comprehension, lacking the capacity to consent and a known cancer recurrence. Prostate cancer patients at three oncology departments across the UK were screened for late gastrointestinal effects of pelvic radiotherapy using the ALERT-B screening tool and GSRS. Patients identified with gastrointestinal symptoms were then referred to a new gastroenterology service. Between June 2015 and January 2016 questionnaire responses from 164 prostate cancer patients recruited to the EAGLE study were analysed. The ages of men recruited ranged from 54 to 87 years with a mean age of 73 years. The validation phase as part of the EAGLE study was approved by North West Liverpool East REC (reference 14/NW1206).

Validation of ALERT-B was analysed in terms of internal consistency reliability, item-scale correlation coefficients and factor analysis. Internal consistency reliability was assessed by determining the Cronbach's α coefficient with $\alpha \geq 0.6$ – 0.7 indicating (broadly) adequate levels of reliability. Item data were not normally distributed and so the Spearman rank correlation coefficient ρ of each item score with respect to the mean value for ALERT-B was determined. Values for the item-scale correlation coefficient that

were ≥ 0.6 were taken to indicate high levels of consistency for the item.

An additional analysis used exploratory factor analysis [24,25] of both GSRS and ALERT-B to identify highly correlated items. However, this analysis is not discussed at length here due to size considerations of this article, although results for factor loadings from this analysis are available as [Supplementary Material](#).

Results

Phase One

The first draft of the screening tool was generated (Figure 2) during the first expert consensus meeting. Screening tool items were selected for immediate clinical relevance with the intention that a 'yes' response to any single item would trigger clinical consideration for a referral to gastroenterology.

Phase Two

In total, 12 participants were interviewed during phase two. Table 1 details the age and diagnosed malignancies of the participants. The ages at which participants' pelvic malignancies were diagnosed ranged from 35 to 74 years, with a mean age at diagnosis of 60 years. Just under half the sample ($n = 5$) had been diagnosed with prostate cancer.

Overall, participants were positive about the ALERT-B screening tool and provided suggestions for screening tool refinement, including adjustments to the wording and layout. The main issues and solutions covered in the interviews are outlined and evidenced below with interview excerpts as illustrative examples. All excerpts are fully anonymised. A summary of the findings is presented in Table 2.

1. Do you have difficulty in controlling your bowels, such as:
 - Needing to go straight away/can't wait
 - Having to get up at night to poo
 - Having accidents, such as soiling
2. Do you have bleeding from your bottom?
3. Have you had to adapt your lifestyle because of your bowel or tummy symptoms?

(e.g., do you avoid any activities or situations- travel, work, social life or hobbies? Do you take continence supplies, spare clothing or a radar key with you when you go out? Have you made any dietary changes? Have your symptoms affected any caring duties?)
4. Do your bowel and tummy problems affect your mood, social functioning or relationships?

Fig 2. Version 1 of ALERT-B screening tool questions. Version 1 of the ALERT-B screening tool consists of four questions with 'yes' or 'no' responses. The questions were designed to identify gastroenterology symptoms that are suitable for referral to a gastroenterologist.

Table 1
Qualitative interview participants

Participant demographics	No. participants	
Age	≤59 years	1
	60–69 years	7
	≥ 70 years	4
Malignancy	Prostate	5
	Endometrial	2
	Uterine	2
	Cervical	1
	Anal	1
	Liposarcoma	1
Cancer treatment	Radiotherapy alone	1
	Radiotherapy and surgery	7
	Radiotherapy and hormonal treatment	3
	Radiotherapy and chemotherapy	1

Table 2
Summary of findings presented at the second consensus meeting in phase three

Screening tool feedback	Participant experiences
<p>Screening tool question 1: Do you have difficulty in controlling your bowels, such as: needing to go straight away/can't wait, having to get up at night to poo, having accidents such as soiling.</p> <ul style="list-style-type: none"> • Use of colloquial language in the question helped participants to answer the question (Participants 5; 8); • The sub-questions helped participants to consider their bowel control (Participants 1–12). 	<ul style="list-style-type: none"> • Difficulties in bowel control was a commonly reported symptom during the interviews (Participants 1–6; 8–11); • Participants had no difficulty recalling their symptoms due to concerns about their ability to control their bowels (Participants 1; 3–5; 7; 9–12).
<p>Screening tool question 2: Do you have bleeding from your bottom?</p> <ul style="list-style-type: none"> • Differences in answer threshold emerged as to when a participant would indicate they had rectal bleeding on the screening tool (Participants 2; 5; 6); • For clarity the question could stipulate that any amount or frequency of blood should prompt a yes answer (Participant 9). 	<ul style="list-style-type: none"> • Rectal bleeding was considered a frightening concept (Participant 6); • Participants described an increase awareness in looking for rectal bleeding following their cancer diagnosis (Participant 6); • A fear of missing blood in the stool was reported (Participant 9).
<p>Screening tool question 3: Have you had to adapt your lifestyle because of your bowel or tummy symptoms? (e.g. do you avoid any activities or situations - travel, work, social life or hobbies? Do you take continence supplies, spare clothing or a radar key with you when you go out? Have you made any dietary changes? Have your symptoms affected any caring duties?)</p> <ul style="list-style-type: none"> • Uncertainty over a radar key (Participants 2; 6; 7; 10); • Uncertainty over the inclusion of caring duties in the question (Participants 5; 11); • The list of adaptations helped focus answers (Participants 1–12). 	<ul style="list-style-type: none"> • Suffering from bowel symptoms had resulted in a change in lifestyle and activities (Participants 1–12); • Experiences of social isolation (Participants 1; 2; 4; 8; 9; 11; 12); • Cancer diagnosis may result in positive health behaviour changes (Participant 5).
<p>Screening tool question 4: Do your bowel and tummy problems affect your mood, social functioning or relationships?</p> <ul style="list-style-type: none"> • Uncertainty over the term 'social functioning' (Participant 2); • The question was considered important as suffering from bowel symptoms can have a great impact on social functioning (Participants 1–12); • Even though the question covers a sensitive subject it is still important to ask (Participants 1–12). 	<ul style="list-style-type: none"> • Symptom burden affected mood, relationships and general wellbeing (Participants 1–12); • Relief at the opportunity to discuss symptom impact (Participants 3; 5; 6; 8; 10);
<p>Overall comments</p> <ul style="list-style-type: none"> • Increase font size (Participant 6); • Reformat the tool to make it more visually appealing (Participant 6); <p>Include an explanatory note to contextualise the screening tool (Participant 5).</p>	

Phase Three

A summary of the main findings from the cognitive interviews was used to refine the screening tool during the final consensus meeting in phase three. Each question and the overall layout were reviewed in turn until the final version of the ALERT-B screening tool was agreed. Attendees of the final consensus meeting decided to remove the urgency question as it was thought this would have an impact on daily life and would be covered by the final question. A summary of the modifications can be seen in Table 3, and the questions in the final version of the screening tool in Figure 3.

Phase Four

The final version of the ALERT-B screening tool, as seen in Figure 3, was psychometrically validated against GSRS. In total, 164 patients completed ALERT-B and GSRS. Missing data made up less than 2% for all items. The reliability of the scales for GSRS established using Cronbach's α were found to be: abdominal pain ($\alpha = 0.29$), reflux ($\alpha = 0.74$), diarrhoea ($\alpha = 0.79$), indigestion ($\alpha = 0.79$) and constipation ($\alpha = 0.55$). The reliability of ALERT-B was found to be $\alpha = 0.61$. Item-scale correlations using Spearman's correlation coefficient (ρ) for ALERT-B were: 'get up at night to poo' ($\rho = 0.67$), 'accidents, such as soiling or wet wind' ($\rho = 0.76$), 'blood from your bottom' ($\rho = 0.61$) and 'bowel or

tummy problems affecting your daily life' ($\rho = 0.70$). The correlation matrix for GSRS scales and items in ALERT-B is shown in Table 4. The strongest correlations are generally significant between items in ALERT-B and the bowel-related scores, as shown in Table 4.

Spearman correlation coefficients between ALERT-B items and the GSRS abdominal pain, diarrhoea and constipation scales are of generally moderate strength (i.e. of order: $\rho = 0.3$ – 0.5) and they are statistically significant (i.e. $P < 0.05$). By contrast, Spearman correlation coefficients between ALERT-B items and the other GSRS scales (the GSRS reflux scale, in particular) are often smaller in magnitude and they are not always statistically significant (i.e. $P > 0.05$). Finally, results of exploratory factor analysis were found to agree with these analyses of correlation coefficients presented in Table 4. In particular, ALERT-B items were found to correlate strongly only with items in the GSRS scale that relate to bowel symptoms. However, we note that factor analysis is not discussed in detail here, although a table of factor loadings is available in the Supplementary Material.

Discussion

This study showed that the ALERT-B screening tool was considered by participants to offer an effective way to inform healthcare professionals of their bowel symptoms to

Table 3

An overview of the development of the ALERT-B screening tool from phase three of the study

Wording used in version 1 of the screening tool	Suggested change	Finalised screening tool post-consensus meeting
1. Do you have difficulty in controlling your bowels, such as: <ul style="list-style-type: none"> • Needing to go straight away/can't wait; • Having to get up at night to poo; • Having accidents, such as soiling. 	<ul style="list-style-type: none"> - Define the term 'difficulty in controlling your bowels'. - Clarify the terms 'accidents' and 'soiling'. - Remove 'needing to go straight away/can't wait' from question one. 	1. Do you have any difficulty in controlling your bowels (having a poo), such as: <ul style="list-style-type: none"> • Having to get up at night to poo; • Having accidents, such as soiling or a sensation of wetness ("wet wind").
2. Do you have bleeding from your bottom? 3. Have you had to adapt your lifestyle because of your bowel or tummy symptoms? (e.g. do you avoid any activities or situations - travel, work, social life or hobbies? Do you take continence supplies, spare clothing or a radar key with you when you go out? Have you made any dietary changes? Have your symptoms affected any caring duties?)	<ul style="list-style-type: none"> - Clarify that participants should answer yes for any amount of rectal bleeding, even if it is once. - Remove radar key and caring duties from the list of examples. - Avoid use of the term lifestyle. 	2. Have you noticed any blood from your bottom recently? (any amount or frequency) 3. Do you have any bowel or tummy problems that affect your mood, social life, relationships or any other aspect of your daily life? (e.g. do you avoid any activities or situations - travel, work, social life or hobbies? Do you take continence supplies or spare clothing with you when you go out? Have you made any dietary changes? Do you need to allow for frequency or urgency of needing the toilet?)
4. Do your bowel and tummy problems affect your mood, social functioning or relationships?	Merge question 3 and 4 together.	Question 4 removed.

education, current illness and medication [28–31]. Furthermore, research has shown that cognitive interviews are limited by participants' ability to articulate and discuss their thought processes [32]. Where participants did not report any difficulties with a particular question of the screening tool, it is still not possible to infer that all participants understood the question in the same way [32]. Another limitation is that the patients who responded to the invitation to participate in the study may have been a self-selected group who were willing to discuss their bowel symptoms. Consequently, the sample may not be fully representative of patients with late bowel effects following pelvic radiotherapy.

The validation of ALERT-B has been successful. As expected, values for Cronbach's α for GRSR scales are generally high, with only the abdominal pain scale somewhat lower, as seen elsewhere [16,21]. Cronbach's α was found to be given by $\alpha = 0.61$ for ALERT-B, which is slightly lower than the generally accepted cut-off for 'adequate' given by a value of $\alpha \geq 0.7$. However, it is well known that Cronbach's α is strongly affected by the number of items included in the calculation (with higher numbers of items tending to increase the value of α) and so this value probably does indicate 'adequate' levels of reliability for the three items in ALERT-B. Furthermore, item-scale correlations were high, $\rho > 0.6$, and so these results again indicate broadly that ALERT-B is internally consistent. The correlation matrix of GRSR scales with ALERT-B items indicated that strongest correlations occurred between GRSR diarrhoea scale and the items in ALERT-B, whereas the weakest correlations occurred between GRSR reflux scale and the items in ALERT-B. These results make sense because ALERT-B deals only with bowel problems. Hence, validity is established for both convergent and discriminative validity.

Results of exploratory factor analysis support those results of the analysis of correlation coefficients discussed above. In particular, factor analysis showed that the GRSR reflux scale tends to have the weakest correlations with the items in ALERT-B. Again, this result is explicable as ALERT-B only focusses on bowel symptoms. Factor analysis also showed that ALERT-B 'Bowel or tummy problems affecting your daily life' correlates strongly within many of the items in GRSR and also ALERT-B, and is suggestive of how different gastrointestinal symptoms might influence the patients' daily lives. However, exploratory factor analysis was not discussed in detail in this article, although a table of factor loadings is available (see [Supplementary Material](#)). Work carried out across the four phases has designed, tested and validated the ALERT-B tool. Using mixed methods across two studies has helped to develop and robustly test a new screening tool that is tailored to the needs of this patient group. The questions developed through the consensus group meetings and patient feedback have created a patient friendly screening tool that is largely similar to the clinical questions suggested by Andreyev *et al.* [2]. Participants who were cognitively interviewed felt this screening tool would help to initiate discussions with healthcare professionals about their bowel symptoms.

Conclusions

This study designed, tested and validated the ALERT-B screening tool that was acceptable to patients. The range and content of the questions offer clinicians an understanding of the impact the symptoms have on patients' quality of life and highlight red flag symptoms that require further discussion with the patient. The study also highlights the importance of routinely screening all patients for bowel symptoms in the post-pelvic radiotherapy treatment phase to enable appropriate management to occur.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clon.2016.06.004>.

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