Commonly prescribed drugs and association with breast, colorectal and lung cancer progression: a nested case-control study

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1.0 Background:

There is amassing evidence that commonly prescribed cardiovascular medications such as beta-blockers, angiotensin converting enzyme inhibitors and angiotensin II type I receptor blockers and analgesics such as non-steroidal anti-inflammatory drugs and aspirin may have unintended positive consequences in relation to cancer therapeutics and chemoprevention [1]. The following paragraphs outline the versatile properties of these drug classes and collate the epidemiological evidence from studies of their use in lung, colorectal and breast cancer patients. Given that many of these drugs already attenuate the morbidity and mortality of cardiovascular disease, the leading cause of death in the developed world, their use in cancer prevention is very appealing and warrants further investigation.

1.1 Non steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are commonly prescribed analgesics for the relief of pyrexia, musculoskeletal pain and inflammation but in recent years chronic use of both cyclooxygenase-2 (COX-2) non selective inhibitors (i.e.: aspirin and ibuprofen) and selective COX-2 inhibitors (i.e.: celecoxib) has been shown to reduce the risk of several cancers including colorectal, breast, lung, pancreatic, oesophageal and prostate [2, 3]. COX inhibition is hypothesized to be just one mechanism through which NDSAIDs may reduce cancer risk. COX is an enzyme important in the formation of prostaglandins, prostacyclin and thromboxane; pharmacological inhibition of prostaglandin synthesis has been shown to inhibit tumour proliferation [4]. Other anti-cancer effects of NSAIDs include the inhibition of apoptosis, reduction in angiogenesis through reduced vascular endothelial cell growth factor (VEGF) expression and NSAID induced inhibition of tumour metastasis [5]. Although the chemopreventative and therapeutic interventions of NSAIDs in cancer are obvious, much controversy still surrounds their cardiovascular safety [6-9].

1.1.1 NSAIDs and cancer incidence

A recent meta-analysis of 38 studies [10] (18 cohorts, 16 case-control, 3 nested case-control and 1 clinical trial) has shown that use of any NSAIDs resulted in a 12% reduction in breast cancer (BC) risk RR 0.88 (95%CI 0.84, 0.93). Associations were similar irrespective of the type of NSAID taken, but neither a higher dose nor longer duration of use was associated with a greater reduction in BC risk. Much stronger associations have been seen with regular NSAID use and colorectal cancer (CRC). In 2007, a systematic review of NSAIDs and the prevention of CRC [11] highlighted a reduction in CRC incidence in both case-control and cohort studies in the region of 30-40% with both non aspirin and

aspirin related NSAIDs. The incidence of colorectal adenoma was also reduced with selective COX-2 inhibitors in randomised controlled trials RR 0.72 (95%CI 0.68, 0.78). Epidemiological evidence regarding the role of NSAIDs in lung cancer prevention remains equivocal. One recent large prospective cohort study has indicated a 41% reduction in lung adenocarcinoma, a finding that was limited to men and long term former smokers [12]. The findings of an earlier cohort study of postmenopausal women reported that neither aspirin nor other NSAIDs reduced risk of lung cancer [13], a conclusion shared by two further nested case control studies [14, 15]. However several case-control studies have largely corroborated reduced risk of lung cancer with regular aspirin or NSAID use in the region of 30-60% [16-18]; only one study did not support this association [19] and one study reiterated a stronger effect in ever smokers [17].

1.1.2 NSAID use and cancer progression

The majority of studies thus far have examined aspirin and NSAIDs in relation to cancer incidence; there have only been three observational studies to date that have examined the effect of NSAIDs on cancer mortality and progression. Blair *et al* [20] using data collected on self-reported NSAID use in a prospective study of 591 postmenopausal women (the Iowa women's Health Study) observed a reduction in all-cause and BC mortality amongst women reporting any versus no use of NSAIDs multivariable adjusted HR 0.57 (95%CI 0.40-0.81) and HR 0.64 (95%CI 0.39-1.05) respectfully. An increased frequency of use was not associated with a reduction in mortality. In a further prospective cohort Kwan *et al* [21], examined self-reported NSAID use in relation to breast cancer recurrence amongst 2292 early-stage breast cancer survivors participating in the Life After Cancer Epidemiology (LACE) study. The authors found a significant reduced risk of BC recurrence with ibuprofen RR 0.56 (95%CI 0.32, 0.98) but not aspirin; ibuprofen in combination with other NSAIDs demonstrated a similar inverse association with BC progression. In a more recent prospective cohort study of 4164 female nurses with early stage (I, II or III) BC (the Nurse's Health Study), Holmes *et al* [22] examined the number of days of use per week of aspirin in relation to BC specific mortality. 341 BC deaths occurred during follow-up and the risk of BC death decreased as the frequency of aspirin use increased, RR 1.07 (95%CI 0.70, 1.63), RR 0.29 (0.16, 0.52), RR 0.36 (0.24, 0.54) for 1-2 days/wk, 2-5 days/wk and 6-7 days/wk of aspirin use respectively; similar results were observed for distant BC recurrence in relation to frequency of aspirin use, with daily use according a RR of 0.57 (95%CI 0.39, 0.82). Again however information on NSAID usage was self-reported in this study and no information was provided regarding the dose of aspirin taken. It can be seen therefore that more robust evidence on BC mortality and cancer progression amongst early stage BC survivors may be obtained via an observational study based on the collection of prescription/dispensing data.

Over-expression of COX-2 is found in many cancers including the lung, colon and breast [23, 24], this has been shown to increase the production of eicosanoids such as prostaglandins and thromboxanes which may induce VEGF expression and promote tumour angiogenesis and subsequent tumour growth [25]. It is perhaps unsurprising therefore that increased COX-2 expression has been associated with poorer prognostic characteristics such as lymph node metastasis, higher tumour grading, and increased tumour size and potential for metastasis [23, 26, 27]. Studies in BC patients have shown that among oestrogen receptor positive (ER +ve) individuals, COX-2 expression is predictive of worse prognosis and poorer survival [28]. Aromatase is an enzyme involved in the biosynthesis of oestrogen via the aromatisation of adrenal and ovarian androgen. It is known that aromatase is elevated in tumour as opposed to healthy breast tissue [29] and it has been hypothesised therefore that elevated oestrogen induced by increased aromatase activity may stimulate tumour growth and development [30]. The inducible isoenzyme COX-2 has also been shown to stimulate oestrogen biosynthesis [31] so it can be seen that aromatase and COX-2 pathways are interrelated and that the aromatase-suppressive effects of COX-2 inhibitors may suppress local oestrogen biosynthesis enhancing the effect of aromatase inhibitors (AIs) in oestrogen positive tumours. There have been a number of trials therefore which have evaluated the anti-tumour effects of COX-2 inhibitors in BC and their ability to act synergistically with aromatase inhibitors (AIs). Falandry *et al* [32] conducted a double blind phase three RCT of exemestane plus celecoxib twice daily (400mg) vs. placebo amongst 157 postmenopausal women with no prior AI use. The trial was terminated prematurely given the cardiotoxicity of celecoxib reported in other trials; however the authors noted a trend favouring celecoxib and there were no severe adverse affects reported. In a further randomised phase II study Dirix *et al* [33] investigated the treatment of advanced hormone-sensitive breast cancer patients with daily exemestrane (25mg) alone and in combination with celecoxib (400mg) twice daily, however the authors found similar clinical benefit and time to disease progression in both arms. It would be beneficial therefore to conduct an observational study of early stage breast cancer to assess the efficacy of an AI in combination with a COX-2 inhibitor in the treatment of metastatic breast cancer.

Both aspirin and non-aspirin NSAIDs have been shown to lower the risk of CRC, and recent evidence suggests that NSAID use in patients with colorectal cancer improves cancer-specific and overall survival, particularly in patients with tumours that express COX-2 [34]. Several studies have investigated the effects of NSAIDs in relation to clinical outcomes after CRC diagnosis.

Zell *et al* [35] in a cohort study of female teachers examined pre-diagnostic (and self-reported) NSAID use in relation to CRC mortality. The authors reported that any frequency of pre diagnostic NSAID use vs. none was associated with improved overall survival HR 0.71 (95%CI 0.53 – 0.95) and CRC specific mortality HR 0.58 (95%CI 0.40, 0.84). A further prospective cohort study of 1279 men and women with early stage (I, II, III) CRC from the Nurses' Health Study and the Health Professionals Follow-up study found that compared with non users, individuals who regularly used aspirin after diagnosis experienced a lower risk of CRC mortality HR 0.71 (95%CI 0.53, 0.95) and all cause mortality HR 0.79 (95%CI 0.65, 0.97); particularly amongst individuals whose tumours over expressed COX-2, where a 60% risk reduction was observed. Examining the effect of aspirin and NSAIDs on the risk and survival from CRC Din *et al* [36] conducted a large population based case-control study in Scotland of 2279 CRC cases and 2907 age, gender and residential area matched controls. Pre-diagnostic use of low-dose aspirin (>4 days/wk for 1 month of more) was not found to be associated with all-cause or CRC-specific mortality. Recently Rothwell *et al* [37] examined deaths due to cancer during and after randomised trials of daily aspirin vs. control in eight trials originally established for the prevention of vascular events. The authors collected individual patient data from seven trials, 23,535 patients (657 cancer deaths) and found that allocation to aspirin reduced all cancer mortality by 34%; in a sub-analysis of cancer site, daily aspirin use was associated with a 22% reduction in CRC-specific mortality with this risk improving to a 59% reduction with increased duration of treatment. Analysis on longer follow-up durations i.e.: 10-20 years of follow-up time (179 CRC deaths) demonstrated marked increases in CRC survival HR 0.51 (95%CI 0.35, 0.74; pvalue <0.001). In the same study LC specific mortality was reduced by 29% HR 0.71 (95% 0.58, 0.89; pvalue 0.002), an analysis based on 326 LC deaths. Fuchs *et al* [38] prospectively studied 830 patients with stage III CRC enrolled in a randomised trial of post-operative adjuvant chemotherapy. 72 patients were defined as consistent aspirin users (continuously using at half way point and again at 6 months) and compared to non aspirin users had a HR of 0.45 (95%CI 0.21, 0.97) for disease recurrence, a HR of 0.48 (95%CI 0.24, 0.99) for disease recurrence/death and a HR of 0.52 (95%CI 0.19, 1.46) for death. Midgley *et al* [39] conducted a phase III randomised trial assessing rofecoxib in the adjuvant setting of CRC. Unfortunately the study was affected by the worldwide withdrawal of rofecoxib, however some 1167 patients received the intervention and a further 1160 received placebo (mean follow-up 4.85 yrs), with 241 and 256 CRC deaths and 297 and 329 CRC recurrences in each arm respectively. There was no difference in all cause or CRC specific mortality between the two arms and COX-2 expression was not associated with poorer prognostic or predictive effects, though as latter studies have shown this study may not have had a long enough latency period for the optimum effect of NSAIDs to occur.

1.2 Bisphosphonates

1.2.1 Bisphosphonates and cancer progression

Bisphosphonates are the pharmacologic treatment of choice for preventing reduced bone mineral density (BMD) and fractures amongst postmenopausal women [40] and are therefore commonly prescribed in the treatment of osteoporosis/osteopenia [41, 42], but they have additional use in the treatment of hypercalcemia and the prevention of bone metastasis and other conditions involving bone fragility [40, 43, 44]. BC has a prodigious capacity to metastasise to bone and therefore skeletal metastasis is common in advanced disease [45]. Bone undergoes constant turnover (homeostasis) regulated by the functions of two bone cells osteoblasts and osteoclasts. Osteoblasts are responsible for bone formation and are essentially adapted fibroblasts which express genes for bone sialoprotein and osteocalcin. Osteoclasts permit bone resorption by destroying the mineralised matrix of the bone. Bisphosphonates inhibit the action of osteoclasts by preventing their formation, diminishing their activity or by encouraging their apoptosis, effectively slowing bone loss [40].

The potential anticancer effects of first generation bisphosphonates such as clodronate i.e.: non-nitrogen containing bisphosphonates were reported by Powles *et al* [46] who conducted a randomised double-blind multicenter trial of oral clodronate (1,600 mg/day) vs. a placebo over a two year period starting within two months of primary treatment of 1,069 operable (stage 1-3) breast cancers. The authors found a significant reduction in the occurrence of bone metastasis amongst those in receipt of clodronate HR 0.44 (95%CI 0.22, 0.86) however the effect was limited to the treatment period with a non-significant but borderline reduction observed during the total follow-up HR 0.77 (95%CI 0.56, 1.08) but there was a statistically significant overall reduction in mortality. Interestingly the authors also noted a significant reduction of non-osseous metastasis in the treatment arm. In a subsequent survival analysis of the same participants [47] with a mean of 5.6 years of follow-up, the authors confirmed that oral clodronate significantly improved the five year bone relapse free survival in all patients over the five year study period HR 0.69 (p=0.04) with differences most pronounced in patients with stage II/III disease. In a similar prospective randomised controlled study Diel *et al* [48], assessed the addition of clodronate (1600 mg/day) for two years or no treatment along with standard adjuvant breast cancer treatment amongst 290 patients. The authors reported a significant improvement in overall survival in the clodronate group with 20.4% of patients in the intervention arm dying in the 8.5 years of follow-up vs. 40.7% of control patients. However significant reductions of bony and visceral metastasis were no longer seen at 36 and 55 months follow-up. In contrast other trials have found no clinical benefit of clodronate in terms of metastasis prevention or an improvement in survival [49].

In recent years a variety of preclinical and clinical studies have illustrated that the action of nitrogen containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) go beyond preventing osteoclast-mediated bone resorption and have demonstrated anti-cancer activity. For instance in vitro studies have shown that bisphosphonates inhibit tumour cell adhesion and invasion, induce tumour cell apoptosis, reduce tumour cell viability and proliferation and exhibit anti-angiogenic effects [50]. There is also recent evidence to suggest that there is a synergistic anti-cancer effect of adjuvant bisphosphonate in combination with chemotherapeutic agents in breast cancer patients [51]. Emerging evidence from RCTs suggests that both oral and intravenous nitrogen containing bisphosphonates may reduce breast cancer recurrence. For instance Brufsky *et al* [52] in an analysis of the interim (12 month) results of 1,667 women from two on-going trials, Z-FAST and ZO-FAST (Zometa-Femara Adjuvant Synergy Trial), found that the group of women who had received zoledronic acid concurrently with letrozole (upfront) vs. those who had not received the drug until after bone loss had become clinically significant (delayed) had a significantly lower rate of cancer recurrence (secondary study end point), 0.84% vs. 1.9% (p=0.04). In a further analysis of 36 months of follow-up from this trial, Eidhmann *et al* [53] reported a 41% reduction in disease-free survival events amongst those receiving zoledronic acid plus adjuvant letrozole compared to those receiving letrozole alone HR 0.59 (95%CI 0.36, 0.96). Gnant *et al* [54] in an analysis of 1803 premenopausal women with endocrine responsive early stage breast cancer in the Austrian Breast and colorectal cancer study group trial (ABCSG) who were randomised to receive subcutaneous goserelin (oestrogren suppressant) (3.6 mg every 28 days) plus tamoxifen (oestrogen receptor antagonist) (20mg per day orally) or anastrozole (AI) (1mg/day orally) with or without zoledronic acid (4mg intravenously every 6 mths) for 3 years, showed that the addition of a bisphosphonate to the endocrine therapy vs. endocrine therapy alone resulted in a 36% reduction in the risk of disease progression HR 0.64 (95%CI 0.46, 0.91) but did not impact on overall mortality HR 0.60 (95%CI 0.32, 1.11). In both studies the addition of bisphosphonate reduced disease recurrence in both bone and non-bone sites such as the contralateral breast; an effect which has been hypothesised to arise from bisphosphonates beneficial effect on the bone marrow microenvironment in which dormant tumour stem cells would normally survive in early stage disease [55].

In a recent meta-analysis, Mauri *et al* [56], examined published and unpublished RCTs assessing the use of adjuvant bisphosphonate in relation to early stage breast cancer progression. The authors identified 13 eligible trials involving a total of 6886 patients. Adjuvant use of bisphosphonates was not associated with overall mortality OR 0.71 (95%CI 0.48-1.04) or disease recurrence OR 0.84 (95%CI 0.60-1.18); however significant heterogeneity was observed, p=0.34 and p=0.02 for overall

mortality and disease recurrence respectively. In sub group analysis the authors found that zoledronic acid was associated with a 32% lower risk of disease recurrence, but the authors did state that this may have been a consequence of multiple testing. Of note the results of this meta-analysis highlighted a non-significant trend towards better outcomes (fewer bone metastases, deaths and local/distal recurrences) amongst bisphosphonate users vs. non users. This latter finding is in agreement with Rennert *et al* [57] who have reported that women receiving bisphosphonates who developed breast cancer had tumours with better prognostic features, including a lower proportion of human epidermal growth factor receptor – 2 (HER2) positive tumours, compared with women who did not receive bisphosphonates.

Taken as a whole, there is mounting evidence that bisphosphonate therapy for postmenopausal osteoporosis might significantly reduce the risk of breast cancer progression and also aid in the prevention of breast cancer recurrence in women with early-stage breast cancer. Further evidence of reduced progression in early stage breast cancer patients receiving bisphosphonates from observational studies may help generate hypotheses which can then be examined in future prospective randomised studies in this patient group.

1.3 Beta-Blockers

1.3.1 Beta-Blockers and cancer progression

Beta-blockers are a class of drugs which are particularly useful for the management of cardiac arrhythmias, cardioprophylaxis following myocardial infarction and cerebrovascular events and hypertension [58, 59]. Noradrenaline (norepinephrine) and adrenaline (epinephrine), the major neuroendocrine transmitters of the sympathetic nervous system 'fight or flight' response, bind to and activate adrenergic receptors or adrenoreceptors [60]. Beta-2 adrenergic receptors (β_2AR) have been shown to be present on pancreatic, breast and ovarian cancer cells [61] leading some to posit that norepinephrine may be an aetiological factor in various types of cancer [62]. In addition, in vitro cell line studies of colorectal [63], prostate [64] and breast cancer [65] have shown stimulation of β_2AR via the stress catecholamine hormone norepinephrine to be a potent inducer of cell migration, a prerequisite to metastasis formation; highlighting a role of norepinephrine in cancer progression. Moreover β_2AR stimulation has been associated with resistance to apoptosis [66], and integrin-mediated cell adhesion [67] via exciting the cyclic adenosine monophosphate (cAMP) activating the downstream protein kinase pathway A (PKA) [68] enabling detached cells to survive and migrate. Importantly, β_2AR antagonists such as propranolol have been shown to inhibit norepinephrine-

mediated angiogenesis and metastasis in vitro [63, 64, 69-71] and in vivo [72-74] and these benefits appear to extend to several cancer sites [75-77].

Thus far, two meta-analyses [78, 79] using data derived from randomised controlled trials have examined the risk of cancer from β-blocker drug use; neither have demonstrated increased or decreased odds of malignancy from this drug class, obtaining pooled ORs of 1.00 (95%CI 0.78, 1.32) and OR 0.94 (95%CI 0.88, 1.00) respectively. Data from non-randomised studies has been just as decisive with most studies reporting no association between use of beta-blockers and breast [80-83] or prostate cancer incidence [84-87]; data at other cancer sites is scarce however inverse associations have been reported with β-blockers and colorectal [87, 88] and head and neck cancer [88]; conversely two studies have accorded an increased risk of renal cell carcinoma [89, 90] with β-blocker use.

The role of β-blockers in cancer progression has been infrequently assessed and is less definitive. Early RCTs had suggested excess cancer mortality in relation to use of β-blockers [91-93], and this was confirmed in a meta-analysis of these three trials [94]; however, subsequent studies have refuted this showing β-blocker users to experience similar cancer mortality as non-users [95-97] a finding supported by a more recent meta-analysis of six RCTs [78] pooled OR 1.02 (95%CI 0.92, 1.14). In the most recent investigation amongst 466 patients with early stage (I & II) primary breast cancers, Powe *et al* [98] found a 71% reduction in breast cancer mortality HR 0.29 (95%CI 0.12, 0.72) and a 57% reduced risk of distant metastasis HR 0.43 (95%CI 0.20, 0.93) comparing β-blockers users vs. non-users; however, this analysis was based on a small number of β-blocker users (n=43). There are currently two clinical trials investigating the preventative role of perioperative propranolol and etodolac (COX-2 inhibitor) in cancer recurrence and progression in patients with breast (http://clinicaltrials.gov/ct2/show/NCT00502684) and colorectal cancer (http://clinicaltrials.gov/ct2/show/NCT00888797) undergoing surgery with curative intent.

Given the potential for adrenoreceptor antagonists to impede cancer progression [99] and mediate prognostic factors [76], a robust epidemiological investigation into the role β-blockers may play in cancer progression is warranted.

1.4 Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and cancer incidence

Recently, it has been suggested that the renin-angiotensin-aldosterone system (RAAS) which is critical in renal and cardiovascular homeostasis, may be implicated in the development of tumours. Angiotensin II is a polypeptide hormone which acts on angiotensin II type I receptors (ATIR) causing blood vessels to constrict, resulting in an increase in blood pressure and as such is thought to play a pivotal role in RAAS [61]. Angiotensin II is converted from angiotensin I by angiotensin converting enzyme (ACE), an enzyme which can be pharmaceutically inhibited via ACE inhibitors (ACEIs). ACEIs and angiotensin II type I receptor blockers (ARBs) are a group of widely prescribed pharmaceuticals that are used primarily in the treatment of hypertension and congestive heart failure, left ventricular systolic dysfunction and to slow the progression to dialysis or transplantation in diabetic neuropathy.

ARBs function by blocking the activation of angiotensin II type I receptors. This is important because angiotensin II is a known growth factor and can stimulate tumour neovascularisation, an important requirement for tumour growth [100, 101] and suppression of this system might prevent cancer progression. In vitro and in vivo studies have demonstrated that ARBs and ACE inhibitors through selective inhibition of ATIRs decrease tumour growth, tumour-associated angiogenesis and metastasis [102, 103] , assuaging the progrowth and proangiogenic effect of angiotensin II [104]. Despite biologically plausible mechanisms, epidemiological studies examining the role of ARBs and ACEIs in the prevention and progression of cancer are limited and results to date have been inconsistent.

Lever *et al* [105] in a Scottish retrospective cohort study examined 5207 patient and assessed the risk of cancer in hypertensive patients receiving ACEIs or other antihypertensive drugs. The RR of incident and fatal cancer among the 1559 patients receiving ACE inhibitors were 0.72 (95%CI 0.55, 0.92) and 0.65 (95%CI 0.44, 0.93) respectively. Examining the incident risk of different types of cancer in users of ACEIs the authors reported a significantly reduced risk of lung cancer RR 0.34 and a borderline significant inverse association with BC RR 0.33 and a non-significant reduction in colorectal cancer RR 0.35; notably all three estimates were based on small participant numbers with only 6 and 3 persons using an ACEI for lung, breast and colorectal cancer respectively.

ACE inhibitor use has also been associated with a reduction in the risk of oesophageal, colon and pancreatic cancer [106] as well as prostate cancer [107]. Other epidemiological studies have failed to find a protective effect for these agents. Interestingly, a recent meta-analysis of randomised controlled trials reported an increase in cancer incidence among regular users of ARBs [108]. A

second meta-analysis refuted these findings but could not rule out a slight increase in cancer risk with combination use of ARBs and ACEIs [109].

1.4.1 ACEI and ARB and cancer progression

Wilop *et al* [110], retrospectively assessed long-term medication with ACEIs and ARBs amongst 287 patients with advanced non-small cell lung cancer undergoing chemotherapy. In multivariate analysis patients receiving either ACEIs or ARBs vs. non-recipients survived a median of 3.1 months longer HR 0.56. A further study by Chae *et al* [111], investigated the association between use of ACEIs or ARBs and the risk of tumour recurrence amongst asymptomatic BC patients (stage I-III). 23% of non-users developed a recurrence over a mean of 4.4 years follow-up vs. just 14% amongst users OR 0.54 (95%CI 0.33, 0.97). Five year disease free survival was also significantly higher in ACEIs/ARBs users vs. non-users; in addition use was associated with a reduction in mortality amongst a subset of patients with hypertension OR 0.41 (95%CI 0.23, 0.80) but not amongst all breast cancer patients. Overall, there is growing evidence that use of ACEIs and ARBs are associated with a reduced risk of cancer recurrence, however the number of patients treated with ACEIs/ARBs in these studies has been quite small. Larger observational studies are needed to compile evidence for the conduct of a more robust prospective randomised trial.

1.5 Northern Ireland enhanced prescribing database (NIEPD)

Under the provision of the National Health Service (NHS) in Northern Ireland (NI), all prescription medications are dispensed free of charge to the entire population, irrespective of age or means. Uniquely within the UK, in 2008 in NI the Business Services Organisation (BSO) implemented an Enhanced Prescribing Database (EPD) recording prescription and dispensing processes through the use of two-dimensional barcode technology. A prescription is generated electronically by the initial prescriber (the patient's GP) and printed onto the usual paper script. However each script is encoded with a 2D barcode (XML) containing the patient's name, address, postal code, date of birth, age, Health & Care number (H&C), GP's name, surgery name/address, name of the drug(s), instructions of use (one a day etc.), date of issue and the dose and quantity of the drug to be supplied. Ultimately it is intended that scripts will be scanned by community pharmacists when the patient or a nominated representative presents the script for collection of the medication, automatically collecting dispensing data. However at present the 2D barcodes are scanned at BSO when they are received from all pharmacies across NI at the end of each month. Thus whilst this offers assurance that prescriptions written by the GP have been dispensed, there is as yet no way of assessing individual compliance and usage of this medication. At present approximately 90% of all prescriptions scanned

at BSO results in useable data in EPD. A central database of prescribed and dispensed drugs for approximately 1.9 million patients registered with a GP in NI now exists in BSO for use by healthcare professionals and researchers.

1.6 Northern Ireland Cancer Registry

The Northern Ireland Cancer Registry (NICR) was established in 1994 and uses an automated computer system with multiple information sources to collate information on new diagnoses of cancer, with information collected for incidence from 1993 onwards. The three main sources for registration are the Patient Administration System (PAS) used by all hospitals, histopathology reports and death notifications which are supplied by the General Registrar Office (GRO). From PAS, the registry obtains demographic information on individual patients along with basic site and behaviour information (benign or malignant) for each tumour. This information is supplemented by electronic downloads from histopathology and cytopathology laboratories i.e.: specification of histological tumour grade (specifies degree of cell differentiation and is an indicia of tumour aggressiveness) and morphology (microscopic histopathological diagnosis by a pathologist). A major focus of the registry's work is on the verification of information from a single hospital admission, a single histopathology report or a single death certificate (death initiated cases). Trained Tumour Verification Officers (TVOs) examine general practitioners' (GPs) notes for patients who have died from cancer, hospital records for cases identified without histopathology or cytology confirmation and histopathology reports where there is conflicting information or other possible errors. Follow-up of patients is conducted passively by linking cancer incidence data to death certificate information. Data on cancer mortality also comes from the information supplied by GRO.

1.6.1 Treatment and tumour staging

Surgical, chemotherapy and radiotherapy data is accessible in the NICR through the Clinical Oncology Information System (COIS), which is electronically derived via a dedicated client server in the Belfast City Hospital (Citrix Metaframe). Staging is carried out using a number of laboratory and clinical tests at the time of diagnosis. The staging classification used in NI is the TNM stage. This includes information on the extent of the primary tumour (T), the absence or presence of lymph node metastasis (N) and the absence or presence of distant metastasis (M). The classification combines these three elements to produce an overall TNM stage for the tumour. However the manner in which the overall TNM stage is derived depends upon the cancer site.

2.0 Plan of investigation:

The proposed investigation will involve establishment of three retrospective cohorts of confirmed BC, CRC and LC cases diagnosed between 2008 and 2011 from the Northern Ireland Cancer Registry (NICR) and subsequent linkage of these cohorts to pertinent prescription and dispensing data held within the Northern Ireland Enhanced Prescribing Database (NIEPD).

2.1 Aims and objectives

To investigate if regular use of non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme Inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), β-blockers or bisphosphonates, defined as ≥ 3 times per week for one month or more, is associated with disease progression in breast (BC), colorectal (CRC) and lung cancer (LC) patients.

Specific hypotheses will be to test whether or not:

- post-diagnostic NSAID use is associated with a reduction in BC, CRC and LC specific or all cause mortality and cancer recurrence
- post-diagnostic ACE inhibitors/ARB use is associated with a reduction in BC, CRC and LC specific or all cause mortality and cancer recurrence
- post-diagnostic β-Blocker use is associated with a reduction in BC, CRC and LC specific or all cause mortality and cancer recurrence
- post-diagnostic bisphosphonate use is associated with a reduction in BC, CRC and LC specific or all cause mortality and cancer recurrence

2.1 Methodology:

2.1.1 Study design

This study will utilise a nested case-control approach to cohort analysis to investigate cancer survival and progression in BC, CRC and LC patients. The process of NICR-EPD data linkage will occur at several time points. This is necessary as there is often several months delay in the recording of cancer incidence and staging information in the cancer registry and a similar lag in the processing of prescriptions returned from community pharmacies at BSO; it is impracticable to conduct the full 3.5 year study follow-up from the study outset. It is envisaged that an initial pilot investigation will be conducted with study follow-up commencing 1st July 2008 till 31st Dec 2010. For a number of subjects, particularly amongst those individuals with early stage disease at diagnosis, follow-up time may be insufficient for study outcomes (cancer deaths/recurrences) to occur. This planned interim

analysis will be repeated when a further year of follow-up data becomes available; study follow-up will therefore run from 1st July 2008 until the 31st Dec 2011 (3.5 years in the main analysis). Data linkage between the NICR and BSO will occur on a total of six occasions at two distinct study phases; three times (once for each cancer site) at the initial interim analysis (constituting an initial pilot investigation) and three times when the study follow-up is complete (main analysis).

Ultimately it is envisaged that this initial study will serve as a comparison to a similar project to be undertaken using data from the General Practice Research Database (GPRD) which is part of a Cancer Research UK application currently under review. Uniquely this study will contain data on cancer treatment which is absent from the GPRD data and will establish a co-morbidity index for the intended cancer sites.

2.1.2 Study population

We plan to establish a cohort of all incident (newly occurring) primary BC, CRC and LC patients diagnosed between 1st July 2008 and 31st Dec 2011 (inclusive) using incidence data obtained through the NICR; follow-up for this study will therefore end on the 31st Dec 2011. Individuals with any stage of BC, CRC and LC will be considered eligible for the study. Male BC patients will be excluded, but both male and female CRC and LC cases will be eligible. Patients aged ≤18 years and those in which a prior cancer diagnosis (other than non-melanoma skin cancer (NMSC)) has been made will also be ineligible.

Approximately 1,500, 1,100 and 1000 incident cases of BC (female only) [112], CRC (all persons) [113] and LC (all persons) were diagnosed in Northern Ireland in 2008. In the NICR for the same year, staging for BC, CRC and LC was 89.5% and 81.7% complete respectively; the percentage of LC patients with available staging information was much lower at 45.6% on average. In terms of stage of disease at diagnosis, in 2006 in Northern Ireland there were 951 incident BC cases, of which 27.9%, 32.4%, 17.8% and 7% were stage I-IV disease respectively [112]. In the same year there were 913 incident CRC cases, 10%, 27%, 26% and 25% of which were stage I-IV (Duke's A-D) disease [113]. 834 incident LC cases were reported in 2006 and 13%, 5%, 16% and 48% were stage I-IV at diagnosis [114].

Therefore given potentially up to 3.5 yrs of study follow-up time (42 months) in each cohort and accounting for the percentage of likely staged cancers in each year, it is estimated that 9455 patients with any stage disease (4700 BC, 3145 CRC and 1610 LC cases) will be available for analysis. Of these 9455 patients, it may be expected that 2820 BC, 1164 CRC and 290 LC cases (4274 cases in total) will be early stage disease (TNM I-II) at the time of their initial diagnosis.

2.1.3 Data sources

All primary incident breast, colorectal and lung cancers diagnosed between the 01/07/2008 – 31/12/2011 will be identified through routinely collected hospital discharge records, pathology reports and oncology notes obtained by the NICR. Data extraction will be undertaken by tumour verification officers employed within the NICR. These individuals will utilise pre-defined data extraction forms to populate each cancer specific database with tumour staging and treatment information as well as data on available confounders for analysis. For instance for breast cancer, (where applicable) fields will be created for the date of diagnosis, date of recurrence date of death and reported cause of death, side (affected breast), site (quadrant), morphology, size, histological tumour grade, lymphvascular invasion, total nodes sampled, total nodes positive, total sentinel nodes involved and the number of sentinel nodes positive, TNM stage, oestrogen receptor status (Q-score), progesterone receptor status (Q-score) and herceptin status. Where available information will also be collected on age, marital status, occupation, parity and breastfeeding status, age at menarche, age at menopause (menopausal status), BMI or body surface area (derived from chemotherapy dose) smoking status, alcohol status, family history of cancer (1^{st} degree relatives), treatment(s) received (surgery, hormone therapy, chemotherapy and radiotherapy) i.e.: for radiotherapy information will be recorded on fractions received, exposure, dose and energy irradiated along with the start and end dates of treatment. Area level measures such as the patient's postcode will also be recorded which will be used to generate a deprivation quintile (described in 2.1.6 below). Study resources will be restricted to NICR staff who have agreed to undertake this duty on behalf of the research team.

In the BSO, it is envisaged that two members of staff (MO'R, PP and RMcL) will be responsible for creating a database of commonly prescribed drugs (Annex 1) – this will be constructed independently of the research team. It is envisaged that the database from the NICR will be linked to the dataset in the BSO via each patient's Health & Care Number using an encryption technique; methods for this process have been detailed in Annex 3. A list of available but irrelevant prescriptions (i.e.: scripts for bandages etc.) from the EPD data is shown in Annex 2. These items will not form part of the NIEPD data download from BSO. As aforementioned, roughly 90% of all prescriptions scanned at BSO result in usable data, however in early 2008 there were several months involving adaptation (printer and software installation throughout GP practices) to the new electronic system wherein a less optimal scan rate may have been obtained. Therefore as a measure of data quality, only those GP practices with a script scan rate of ≥70% will be included in the final study.

A potential ethical issue of this study will be the identification of individuals from data requested in the download. To maximise patient anonymity, patient names and addresses will not be requested in the data download from either BSO or the NICR. What will be requested however is the patient's postcode, this will be used to generate a deprivation quintile based on the socioeconomic demographics of their domicile (as described in 2.1.6 below). As mentioned above this study plans to use each patient's Health & Care number to link the two datasets together. Once matched however this field will be removed from the final dataset as described in Annex 3. The research team recognize that a postcode in combination with gender and date of birth is considered personal identifiable information; for this reason before the final encrypted dataset is received the deprivation quintile will be created and each individual's postcode will no longer be retained. It will therefore not be possible for the research team or others to identify individual patients from the final datasets and patient data will be completely anonymised in any published output.

2.1.4 Outcomes

The principal outcomes are cancer-specific and all-cause mortality in accordance to drug use. Data on the date of occurrence and cause of death will be available via the General Registrars Office (GRO), information that will be obtained under the auspices of the NICR or BSO. Comparison of associations between intended drug exposures and cancer-specific and all-cause mortality will facilitate an assessment of whether any apparent protective effect against cancer progression results from a healthy user effect.

Data on cancer recurrences i.e.: local (in the vicinity of the primary), regional (in surrounding lymph nodes) and metastatic recurrence (spread to another organ/tissue) will be obtained from the NICR prior to linkage of the NIEPD data and will be defined as a relapse of the primary cancer after a period in which no cancer could be detected (this time-frame will vary from site to site and from person to person so cannot be clearly defined). Cancer recurrence will be a secondary outcome measure for this study.

2.1.5 Exposures

The principal exposures of interest will be the use of NSAIDs and aspirin (including low dose aspirin (75mg)), angiotensin converting enzyme Inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), β-blockers and bisphosphonates post-diagnosis of BC, CRC and LC; a generic list of relevant drugs has been detailed in Annex 1. In sensitivity analysis we will exclude NSAID/aspirin use in the first 6 months after cancer diagnosis to assess differences in drugs indicated for pain related to initial cancer symptoms and treatment. Similarly, the sensitivity of excluding common drug use in the 6

months preceding death or disease recurrence (and a corresponding period in matched controls) will be examined to account for drugs used in symptom palliation commensurate with stage of disease (sensitivity analyses will be conducted to investigate the resulting effect size when varying this time interval).

Data derived from the scanned prescription (i.e.: the quantity, dose and frequency of drug use) and the date of prescription will be used to assign a Defined Daily Dose (DDD). DDDs are a validated statistical method of drug consumption maintained by the World Health Organization [115] and can be defined as the assumed average dose per day of a drug used for its main indication in adults.

2.1.6 Covariates

Potential confounders for this analysis may relate to lifestyle factors thought to be associated with BC, CRC and LC survival including, smoking status, alcohol consumption, Body Mass Index (BMI), diet and physical activity level [116-119]. Much of this data can be derived from the Clinical Oncology Information system (COIS) in the NICR for each cancer case. However data on diet and physical activity is lacking and anthropometric data such as height and weight are seldom available. For some patients with rectal or breast cancer who have received radiotherapy, it may be possible to utilise the surface area exposed to radiation as a surrogate for BMI. It's important to remember however that although these aforementioned risk factors may be associated with cancer survival, it is less clear that they will be associated with the drug exposures that are of interest in this study and therefore may not act as true confounders.

Comorbidity may be associated with the use of various drugs, particularly those with a cardiovascular indication, and are therefore also likely to have an impact on mortality and access to treatment. The Charlson co-morbidity index has been used to predict mortality for a patient given a range of co-morbid conditions [120] by assigning a relative weight to each and will be used in the analysis to control for concurrent clinical conditions. Socioeconomic status also has the potential to impact on disease survival possibly modifying health behaviours, access to services and drug exposure. The postcode that accompanies each cancer incidence and mortality record in the NICR will be matched to a Census Output Area (COA) using the Central Postcode Directory (CPD) which is annually updated by the Northern Ireland Statistics and Research Agency (NISRA). The COA will be used as to assign each cancer incidence record with a deprivation score based upon the economic characteristics of all persons usually resident in that area [121]. For the majority of subjects it may also be possible to derive information on occupation from the COIS in the NICR.

Aromatase inhibitors have the potential to induce joint pain which in turn may increase the use of NSAIDs to palliate this symptom. It is also thought that aromatase inhibitors may improve BC survival [122]; as such they are best regarded as both an effect modifier and a confounder. There are several other drugs which will need to be considered as covariates in specific drug analyses, for example bisphosphonate users may have an increased use of NSAIDs to alleviate joint pain and swelling, moreover bisphosphonates may prevent BC progression [56] and so should be considered as confounders in the analysis of NSAIDs.

2.1.7 Statistical Analysis

2.1.7.1 Nested case-control study

The BC, CRC and LC cohorts will be analysed as nested case control studies, the outcome of interest will be death from BC, CRC or LC, all-cause mortality and disease recurrences. The nested case-control design offers a highly efficient epidemiological approach to the assessment of exposure-disease associations and is an established method for computational reduction in comparison to Cox regression [123]. Compared with time-varying survival analysis of cohort data, this method will produce unbiased effect estimates with minimal loss of precision [124] by better controlling for potential confounding variables and improved quantification of exposure with respect to time [125]; moreover the nested case-control design overcomes the issue of immortal time bias [125, 126]. Immortal time bias refers to a period of follow-up in cohort analysis in which study outcomes cannot occur. For example, in a traditional cohort analysis of this study there may be a delay in prescription of a drug (exposure of interest) after the initial cancer diagnosis has occurred (start of study follow-up). Therefore if a case was to die or their cancer was to progress/reoccur before the drug of interest was prescribed, that individual would be misclassified as unexposed. This risks biasing effect estimates in favour of the exposure under study, as a spurious survival advantage may be seen amongst those receiving the drug under observation [126, 127].

Similar analytical strategies will be used in all three cohorts, for example, in the BC specific survival analysis a time-matched nested case-control analysis will be performed. Cases will be defined as cohort members who have died from BC or who have disease recurrence and will be matched to up to 5 patients alive and free of disease recurrence/progression at their time of death (defined as the controls). Controls will be matched on age (in 5-year intervals) and year of breast cancer diagnosis; a form of incidence density sampling which involves matching each case to a sample of those patients who are at risk at the time of case occurrence. Hence the index date for each case will be defined as the date of death/recurrence and this will be allocated to each matched control. The conceptually

relevant drug exposure period for the main survival analysis will be 12 months following BC diagnosis to the 12 months prior to the index date in both the cases and controls.

Conditional logistic regression analyses will be conducted initially to calculate the odds of death and 95%CI for those ever exposed and those never exposed to each of the drugs of interest. Separate analysis will be conducted to examine regular drug use (≥3 times per week for 1 month or more) and duration of use (in DDDs). These analyses will be adjusted for the potential confounders detailed in 2.1.6 above; confounders with missing data will be incorporated using a missing data category. Analyses will be stratified on age, menopausal status (in BC cohort analysis), gender and site (CRC and LC cohorts). Provided the 3.5 year follow-up period is long enough for study outcomes to occur, analyses stratified by cancer stage may also be undertaken.

In order to discern whether associations with NSAID/aspirin use are merely a reflection of a non-specific analgesic effect we plan to assess regular paracetamol use (unassociated with disease progression but with an analgesic effect) and compare these recurrence and survival benefit results. All statistical analyses will be performed using STATA version 11.0 (StataCorp LP, College Station, TX, USA), all tests will be 2-sided with the level of significance set at the 5% level.

2.2 Sample size:

In a recent prospective study in the US, the proportion of breast cancer patients taking aspirin and other NSAIDs regularly (3 or more days/wk) was reported as 27% [20]. During the 3.5 year follow-up period, we would expect 1068 (any stage) breast cancer deaths based on 2008 Northern Ireland female BC mortality data [128]. Conservatively approximating 20% use of NSAIDs amongst breast cancer patients who have not died over the study period we will have approx over 90% power at the 95% confidence level (alpha 0.05, two sided) to detect a 25% reduction in risk of BC mortality in NSAID users vs. non-users.

2.3 Limitations of the study:

A particular difficulty with any pharmacoepidemiology study is the issue of confounding by indication. In observational studies of drug effects there is no randomisation of individuals who are users or non-users of the drug under observation; this is particularly true of widely used over-the-counter and prescription drugs (i.e.: analgesics) as the indication for treatment may be related to prognostic factors or future health outcomes generating an underlying risk profile imbalance. For example, lower Bone Mineral Density (BMD) is an indication for bisphosphonate use but is also associated with lower BC incidence, as lifetime exposure to oestrogen influences not only breast cancer risk but also BMD [129]; therefore BMD and breast cancer risk may be related. Consequently

women in whom bisphosphonate therapy would be initiated might represent a lower risk group for breast cancer than women with normal BMD. This problem may be minimised by controlling for known prognostic factors. Sensitivity analyses of exclusion of observed drug use in the period immediately after cancer diagnosis and in the period preceding cancer death/recurrence will also help reduce this bias. Although 90% of all prescriptions scanned at BSO result in usable data and only GP practices with a script scan rate of over 70% will be included in the final dataset, all analyses will be conducted on the assumption that the medications dispensed from the community pharmacies have been taken as directed; it will not be possible to assess individual compliance with the prescribed medication.

2.4 Project timetable:

Provided that ethical consent and governance approval for this study is granted before 1st July 2011, it is anticipated that the initial stage of this study (extraction of data from NICR) will require 6 months to complete i.e.: a total of 2 months for each of the three cancer sites investigated bringing the study up to January 2012. At this stage follow-up from the cancer cohorts should be from at least 01/07/2008 – 31/12/2010 (pilot investigation). A period of four months will be given to match individual health and care numbers from each of the three NICR datasets to prescription and dispensing data held on the EPD database. From May 2012 a further 6 months will be allotted to compile a further year of follow-up data from the NICR; follow-up for the final stage of this study will therefore run from 01/07/2008 till 31/12/2011 taking the study up to December 2012. Allowing a further 4 months for repeated matching of the NICREPD datasets; by March 2013 both datasets will have been matched. A further 12 months has been set aside for data handling, cleaning, analysis, dissemination and contingency, bringing the study to completion by March 2014 (a 2.6 year project in total).

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Annex 1
Generic names of commonly prescribed drugs in the UK which will be used in the NIEPD_NICR study

NSAIDs:

Indometacin, sulindac, diclofenac, etodolac, acemetacin, accelofenac, piroxicam, tenoxicam, meloxicam, ibuprofen, naproxen, ketoprofen, fenoprofen, fenbufen, flurbiprofen, tiaprofenic acid, dexibuprofen, dexketprofen, mefanamic acid, tolfenamic acid, celecoxib, etoricoxib, lumiracoxib, nabumetone, azapropazone, aspirin

B-Blockers:

Betaxolol, levobunolol, metipranolol, carteolol, Acebutolol, atenolol, atenolol in combination with calcium-channel blocker (i.e.: Beta-Adalat, Tenif), bisoprolol, carvedilol, celipropolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxyprenalol, pindolol, propranolol, sotalol, timolol.

ACE inhibitors:

Captopril, cilazapril, enalapril maleate, fosinopril sodium, imidapril hydrocholoride , perindopril erbumine, quinapril, ramipril, trandolapril, lisinopril, moexipril

Angiotensin-II receptor antagonists:

Candesartan cilexietil, eprosartan, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan, valsartan

Bisphosphonates:

(Oral indications only)

Alendronate, sodium clodronate, disodium etidronate, ibandronate, risedronate sodium, disodium tiludronate

Annex 2

List of BNF codes/ categories to be excluded from EPD data

7.4.4 Bladder Instillations and urological surgery
- 1. Sterile sodium citrate solution for bladder irrigation
- 2.Glycine irrigation solution
- 3. Catheter patency solutions
  - -chlorhexidine 0.02%
  - -sodium chloride 0.9%
  - - Solution G (Uriflex G, Uro-Trainer Twin Suby G)
  - -Solution R (Uriflex R, Uro-trainer Twin Solution R)

9.5.3 Fluoride
- -Tablets
  - En-De-Kay (also oral drops)
  - Fluor-a-day
  - Fluorigard
- -Mouthwashes
  - Duraphat
  - En-De-kay
  - Fluorigard
- -Toothpastes
  - Duraphat

9.6.7 Multi-vitamin preparations
- -vitamin capsules
- -abidec/dalivit drops
- -Forceval
- -Ketovite

12.1.3 Removal of Ear wax
- -almond oil
- -olive oil
- -sodium bicarbonate
- -cerumol
- -exterol
- -Molcer
- -Otex
- -Waxsol

13.2.2 Barrier preparations
13.8.1 Sunscreen preparations
13.8.2 Camouflagers
13.11.1 Alcohols and saline
13.11.2 Chlorhexidine salts
13.11.3 Cationic surfactants and soaps
13.11.4 Iodine
13.11.5 Phenolics
13.11.6 Oxidisers and dyes
14.4 vaccines and antisera

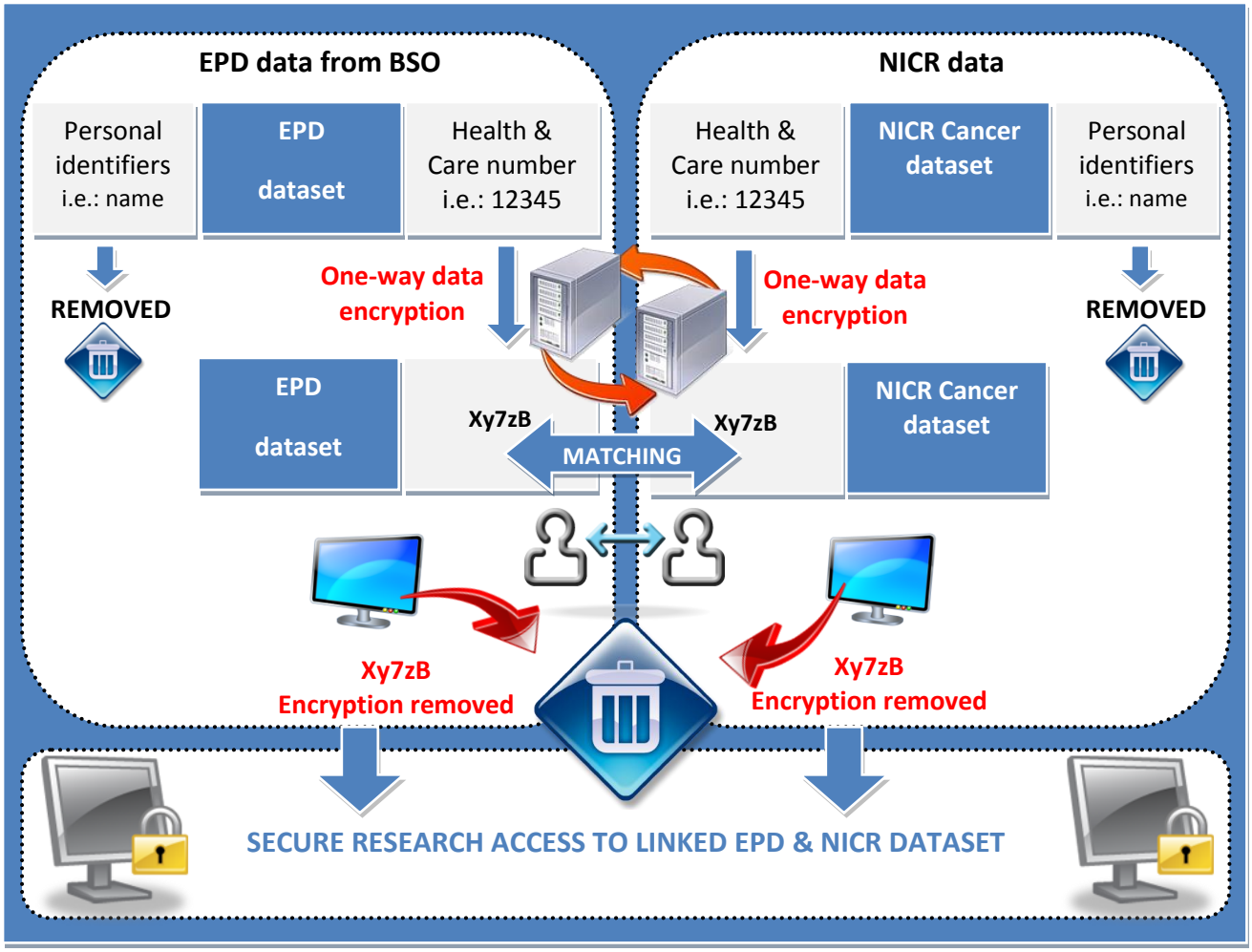
Appendix 7:Nutritional products and gluten free products
Appendix 8:Wound management products and elasticated garments
Ostomy/ urinary equipment as described in the NI Drug Tariff.

Annex 3

One-way encryption process: formation of a pharmacoepidemiology dataset using data from NICR & BSO

An integral component of the NICR-NIEPD data linkage is the use of each individuals Health and Care number as the unique identification field. An important concern and potential ethical issue of the NICR-EPD data linkage is that of data confidentiality and the potential identification of individuals or patients from this field in the final dataset.

We plan to use an Advanced Encryption Standard 256 bit (AES 256) algorithm to conduct a one way encryption of each patient's H&C number, undertaken sequentially on each dataset. The encryption process has been summarised in the flowchart below (Fig 1.0). Briefly, both the NICR and EPD dataset will be saved as a .CSV or comma separated text file with column headings and fed into the data encryption software. The data will be arranged such that the first 10 characters will correspond to each individual's unique H&C number. The encryption process requires two distinct text strings, the first is a password or cipher which forms the basis of the encryption, the second string is additional text which pads the characters out for a more secure encryption. Both text strings will only be known by data custodians in BSO and the NICR where the encryption will be undertaken; without these two strings it is impossible for the researcher to invert the coded data and the process cannot be replicated at a later date. The result is two files containing the new encrypted unique identifier and the remaining variables dissociated from identifiable data. To ensure that the encryption process cannot be reversed on record order each dataset will be sorted in a random order. The two files are then merged using the unique encrypted identifier present on both files before finally removing this field from the final data file. The final file will then be made available to the approved researcher(s) in a secure setting for analysis i.e.: held in a secure office on a password protected PC with access restricted to the intended researcher(s).



AES WINZIP 256 bit encryption & FTP transfer:

An alternative technique to the one-way encryption technique described previously would be to use WinZip v12.0 to perform a 256 bit AES encryption. WinZip's advanced encryption is based on the Rijndael cryptographic algorithm which is certified by the National Institute of Standards and Technology (NIST) in Federal Information Processing Standards (FIPS) Publication 197 as the Advanced Encryption Standard (AES).

WinZip has a customizable password policy which enables configuration of a complex password. For the purposes of this study we could define a minimum password length of 20 characters made up of a range of upper and lower case letters, numbers and symbols. When properly implemented as a key component of an overall security protocol, AES permits a very high degree of cryptographic security, yet is fast and efficient in operation.

The process of encryption is very easy involving only the need to select the encryption method and then to specify a 20 character password. It's envisaged that this encrypted file could then be sent via File Transport Protocol, a standard network protocol used to copy a file from one host to another over the internet. This process will be made safer by using only one dedicated client server. For the purpose of this study it's possible that the encrypted file be sent from one @hscni.net e-mail account to another using the Belfast Health &Social Care Trusts own dedicated server. The sender would then await a response from only the intended recipient acknowledging receipt of the file prior to providing the 20 character password via telephone. Therefore it is only when the intended recipient has received both the password and the data file that the information held within can be unencrypted.

Once at BSO the H&C number on the NICR data file and the BSO data file can be matched prior to deletion and the anonymised dataset passed to the researcher. Of note data will only be sent from the NICR when both the NICR and BSO datasets are ready to be merged, the H&C number matched and identifiable data securely dissociated.