Appendix 1 (as supplied by the authors)

Table S1. Characteristics of the original studies from which patients with suspected adverse drug events were enrolled into the chart review study on repeat adverse drug events.

Study Title	Cohort 1[14]	Cohort 2[16,17]	Cohort 3[15]
Design	Prospective Observational	Prospective Controlled clinical trial	Prospective Observational
Primary Study Objective	To derive a clinical decision instrument to identify patients at high-risk of presenting with an ADE.	To evaluate the impact of emergency department-based pharmacist-led medication review on health outcomes.	To validate clinical decision instruments to identify patients at high-risk of presenting with an ADE.
Study Period	Jul. 1, 2008 - Jan. 31, 2009	Dec. 20, 2011 – Jan. 3, 2013	Sept. 1, 2014 – Aug. 31, 2015
Hospitals	VGH, SPH	VGH, LGH, RGH*	VGH, LGH, OCH*
Participants	**Included** • ≥19 years • Used ≥1 prescription or OTC medication in the past 2 weeks • Spoke English or translator available **Excluded** • Violent behaviour • Intentional self-poisoning • Scheduled revisit • Previously enrolled • Transferred directly to an admitting service • Left AMA	**Included** • ≥19 years • Used ≥1 prescription or OTC medication in the past 2 weeks • Spoke English or translator available • High-risk based on ADE decision rule (Appendix E)[10,11] **Excluded** • Required immediate resuscitation (CTAS=1).[25] • Multisystem trauma • Scheduled re-visit • Sexual assault • Surgical complication • Pregnancy complication • Social problem	**Included** • ≥19 years • Used ≥1 prescription or OTC medication in the past 2 weeks • Spoke English or translator available **Excluded** • Violent behaviour • Intentional self-poisoning • Scheduled revisit • Previously enrolled • Needle stick injury • Sexual assault • Triaged to fast track zone where time to disposition too rapid for enrolment

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			• Transferred directly to admitting service • Left AMA
Enrolment (Appendix B)	Random selection of first patient within hour of start of data collection, subsequent systematic selection of every n^{th} patient	Random selection of first patient within hour of start of data collection, subsequent systematic selection of every n^{th} patient	Random selection of first patient within hour of start of data collection, subsequent systematic selection of every n^{th} patient
ADE definition	"Untoward and unintended event arising from the use of prescription or OTC medications."[13,15,26]	Same as in cohort 1. In addition, medication-related problems were captured and documented.	"Untoward and unintended event arising from the appropriate or inappropriate use of a prescription or OTC medication."
Data Collection Process – for Prospective Cohort Studies (Appendix C)	Trained clinical pharmacist & treating physician independently evaluated enrolled patients for ADEs. An independent committee adjudicated all discordant and uncertain cases by record review.	Clinical pharmacists working in the ED & treating physician independently evaluated enrolled patients for ADEs. Clinical pharmacists and physicians discussed uncertain or discordant cases in ED.	Trained clinical pharmacist & treating physician independently evaluated enrolled patients for ADEs. An independent committee adjudicated all discordant and uncertain cases by record review.
Data Collection Process – for Retrospective Chart Review Study on Repeat ADEs	A clinical pharmacist (uninvolved in any of the prior studies) and a physician reviewed all cases diagnosed with a medication-related problem or ADE in the three prospective studies (Cohorts 1-3). The clinical pharmacist and physician reviewed all medical and research records to ensure consistent application of study definitions, and excluded any cases in which an alternative diagnosis to the ADE had since been made.		
Follow-up Duration	Until ED/hospital discharge, and by telephone follow-up if required	Until ED/hospital discharge, linkage with administrative database for health outcomes	Until ED/hospital discharge, and by telephone follow-up if required
No. Participants	1,591	10,807	1,529

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No. Participants enrolled in current study	1,591	9,913	1,473

VGH=Vancouver General Hospital, a tertiary care hospital in Vancouver, BC, Canada; SPH=Saint Paul's Hospital, a tertiary care hospital in Vancouver, BC, Canada; LGH= Lions Gate Hospital, an urban community hospital in North Vancouver, BC, Canada; RGH=Richmond General Hospital, an urban community hospital in Richmond, BC, Canada; OCH=Ottawa Civic Hospital, a tertiary care hospital in Ottawa, ON, Canada; ADE=adverse drug event; AMA=against medical advice; OTC=over-the-counter; CTAS=Canadian Triage Acuity Score

* We excluded patients recruited into the primary studies at RGH and OCH as we were unable to access their charts for the study on repeat adverse drug events.

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Figure S1. **Patient Enrolment Algorithm**

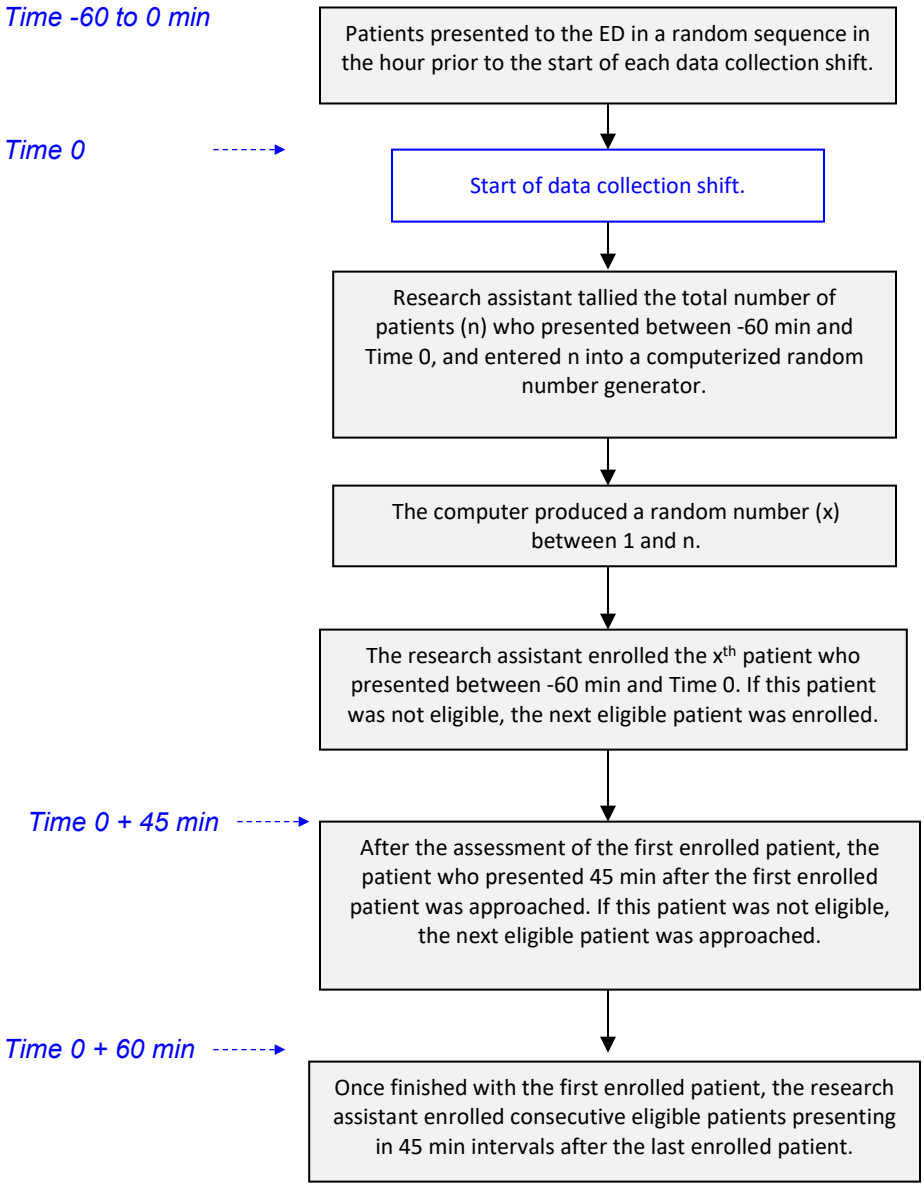

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Figure S2. Adjudication Algorithm for Adverse Drug Events in the Prospective Cohort Studies

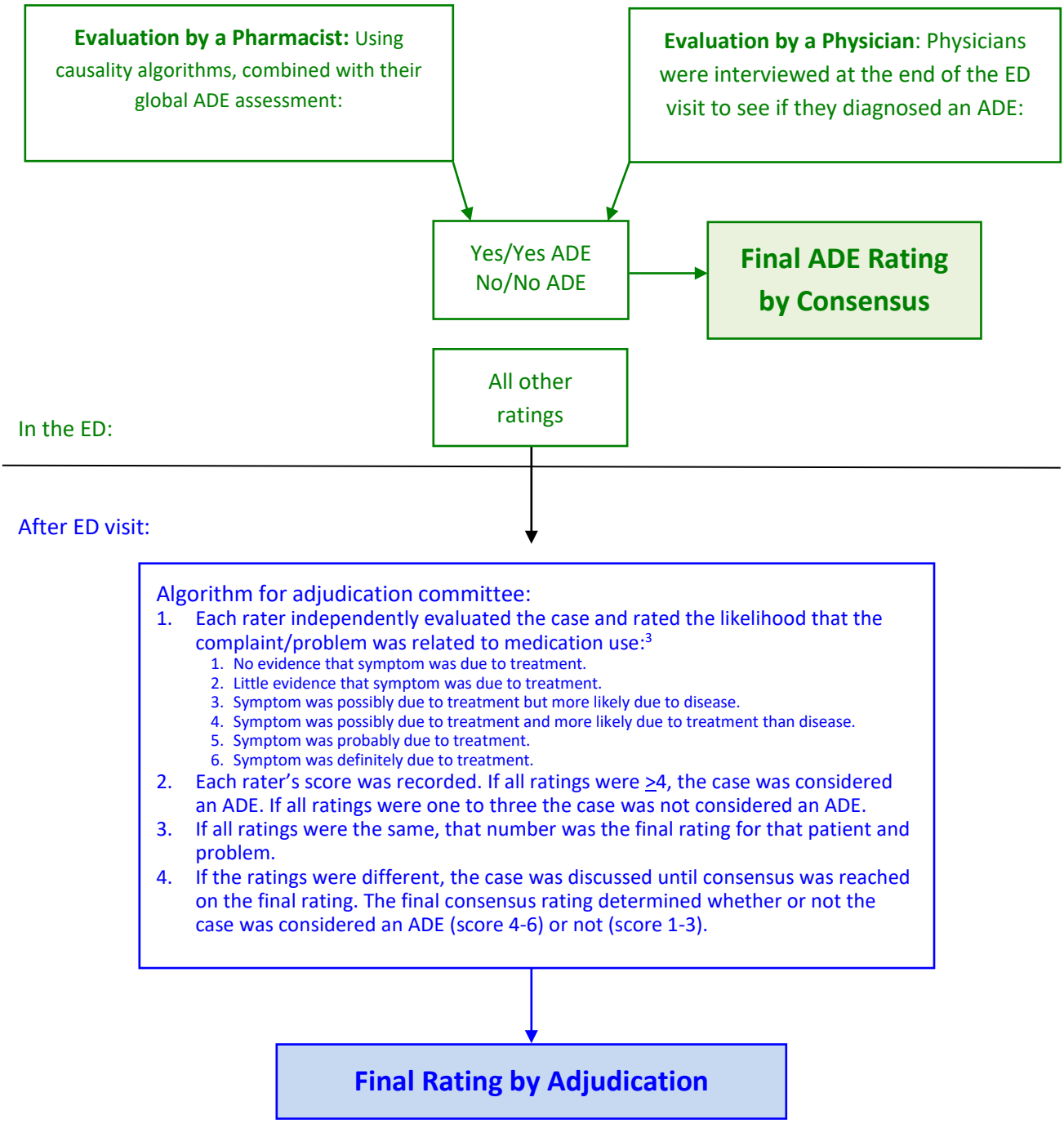

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Table S2. Study Definitions

Adverse Drug Event (ADE):

"Unintended and harmful symptoms, signs or abnormal laboratory values arising from the appropriate or inappropriate use of medications (prescription, over-the-counter or complimentary & alternative medications)." "Harm caused by the use of a drug."

- The sign(s) or symptom(s) are generally *not* deemed to have an alternate explanation by the pharmacist *and* the treating physician. In cases where alternative causes are possible (*e.g.,* fall), the event should only be considered a suspect adverse drug event, if it is likely that the symptom would not have been as severe or not have occurred without the patient being on the drug (e.g., intracranial hemorrhage).
- Abnormal vital signs may constitute an adverse drug event, if the abnormal vital signs meets the cut-offs below, and treating the adverse drug event is medically appropriate according to the treating physician:
    - HR $\leq$ 50 and associated with symptoms (*e.g.,* pre-syncope/syncope, prolonged sinus pauses on ECG)
    - HR $\geq$ 120 and associated with symptoms (e.g., pre-syncope/syncope, chest pain or palpitations)
    - BP $\geq$ 180 SBP or $\geq$100 DBP
- Abnormal laboratory tests can be considered an adverse drug event if they are outside of the hospital's reference range, and treating the adverse drug event is medically appropriate according to the treating physician.
- Harm caused by the use of alcohol or illicit drugs does *not* constitute an adverse drug event.

ADE Classification:

Adverse Drug Reaction (ADR): *"A response to a drug that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease"*

Drug interaction

Dosage Too High

Dosage Too Low

Non-adherence

Inappropriate Drug Withdrawal

Ineffective Drug

Needs Additional Drug/Untreated Indication: This categorization should be reserved for cases in which there is clear previous documentation (*i.e.,* before the index ED visit) in the patient's records about a hard indication for the drug, and lack of contra-indication for treatment.

Transcription/Dispensing/Administration Error

ADE Severity:

Fatal: The adverse event resulted in death.

Severe: The adverse drug event was primary reason for patient's hospitalization, caused permanent disability or was life-threatening.

Moderate: The adverse event required a change in medical management (medical therapy, a diagnostic procedure or consultation)

Mild: No change in medical therapy, including no adjustment of medications required.

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Table S3. Culprit drug and drug class implicated in 1296 adverse drug events				
	Repeat Adverse Drug Events (n=421)		**First Occurrence Adverse Drug Events (n=875)**	
	no.	*% (95% CI*)*	*no.*	*% (95% CI*)*
No. Implicated Medications				
One	318	75.5 (71.4-79.7)	643	73.5 (70.5-76.4)
Two	66	15.7 (12.1-19.2)	162	18.5 (15.9-21.1)
Three	25	5.9 (3.7-8.2)	46	5.3 (3.7-6.8)
More than three	12	2.9 (1.3-4.4)	24	2.7 (1.7-3.8)
Top Culprit Medications				
Warfarin	52	12.4 (9.2-15.5)	105	12.0 (9.9-14.1)
Insulin	34	8.1 (5.5-10.7)	20	2.3 (1.3-3.3)
Hydrochlorothiazide	23	5.5 (3.2-7.7)	42	4.8 (3.4-6.2)
Furosemide	18	4.3 (2.4-6.2)	50	5.7 (4.2-7.3)
Oxycodone	17	4.0 (2.0-6.0)	10	1.1(0.4-1.8)
Hydromorphone	17	4.0 (2.2-5.9)	27	3.1 (1.9-4.3)
Phenytoin	12	2.9 (1.3-4.4)	20	2.3 (1.2-3.3)
Codeine	12	2.9 (1.3-4.4)	32	3.7 (2.4-4.9)

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Ramipril	11	2.6 (1.1-4.1)	23	2.6 (1.6-3.7)
Acetaminophen	11	2.6 (1.1-4.1)	21	2.4 (1.4-3.4)
Quetiapine	11	2.6 (1.1-4.1)	15	1.7 (0.9-2.6)
Top Culprit Medication Classes				
Coumarin derivatives	52	12.4 (9.2-15.5)	105	12.0 (9.9-14.1)
Opiate agonists	51	12.1 (8.9-15.4)	95	10.9 (8.8-12.9)
Insulins	34	8.1 (5.5-10.7)	20	2.3 (1.3-3.3)
Atypical antipsychotics	24	5.7 (3.5-7.9)	36	4.1 (2.8-5.4)
Miscellaneous anticonvulsants	23	5.5 (3.3-7.6)	26	3.0 (1.8-4.1)
Thiazide diuretics	23	5.5 (3.2-7.7)	42	4.8 (3.4-6.2)
Beta-adrenergic blocking agents	20	4.8 (2.7-6.8)	36	4.1 (2.8-5.4)
Adrenals	19	4.5 (2.4-6.6)	38	4.3 (3.0-5.7)
Loop diuretics	18	4.3 (2.4-6.2)	51	5.8 (4.3-7.4)
Angiotensin-converting enzyme inhibitors	13	3.1 (1.4-4.7)	31	3.5 (2.3-4.8)
Benzodiazepines	13	3.1 (1.4-4.7)	26	3.0 (1.8-4.1)

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Top Adverse Drug Event **Symptoms**				
Pain	44	10.5 (7.5-13.4)	59	7.3 (5.7-8.9)
Sub/supratherapeutic INR	41	9.7 (7.6-11.8)	64	7.4 (6.0-8.8)
Hyperglycemia	24	5.7 (3.5-7.9)	39	4.7 (3.3-6.1)
Shortness of breath	19	5.8 (3.7-7.9)	45	5.5 (4.1-6.9)
Hypertension	20	5.4 (3.4-7.4)	26	3.2 (1.9-4.5)
*95% confidence intervals (95%CI) adjusted for clustering of adverse drug event characteristics in patients with multiple events.				

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Table S4. Culprit drug and drug class implicated in 462 adverse drug reactions				
	Repeat Adverse Drug Reactios (n=132)		**First Occurrence Adverse Drug Reactions (n=330)**	
	no.	*% (95% CI*)*	*no.*	*% (95% CI*)*
No. Implicated Medications				
One	95	72.0 (64.2-79.8)	253	76.7 (72.1-81.3)
Two	30	22.7 (15.5-29.9)	52	15.8 (11.9-19.7)
Three	6	4.5 (1.0-8.0)	17	5.2 (2.7-7.7)
More than three	1	0.8 (0.0-2.3)	8	2.4 (1.2-3.6)
Top Culprit Medications				
Hydrochlorothiazide	13	6.4 (3.0-9.8)	40	6.8 (4.8-8.8)
Furosemide	8	3.9 (1.2-6.6)	19	3.2 (1.8-4.6)
Oxycodone	7	3.4 (0.9-5.9)	10	1.7 (0.7-2.7)
Prednisone	7	3.4 (0.9-5.9)	18	3.0 (1.6-4.4)
Ramipril	6	3.0 (0.7-5.3)	14	2.4 (1.2-3.6)
Glyburide	6	3.0 (0.7-5.3)	10	1.7 (0.7-2.7)
Warfarin	6	3.0 (0.7-5.3)	19	3.2 (1.8-4.6)
Acetylsalicylic acid	6	3.0 (0.7-5.3)	27	4.6 (2.9-6.3)

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Cefalexin	5	2.4 (0.3-4.5)	14	2.4 (1.2-3.6)
Top Culprit Medication Classes				
Opiate agonists	14	10.6 (9.0-12.2)	38	11.5 (9.0-14.0)
Thiazide diuretics	13	9.8 (8.3-11.3)	27	8.2 (6.0-10.3)
Beta-adrenergic blocking agents	9	6.8 (5.6-8.1)	4	1.2 (0.4-2.0)
Adrenals	8	6.1 (4.8-7.4)	20	6.1 (4.2-8.0)
Angiotensin-converting enzyme inhibitors	7	5.3 (4.2-6.4)	12	3.6 (2.2-5.1)
Loop diuretics	6	4.5 (3.5-5.5)	13	3.9 (2.4-5.4)
Coumarin derivatives	5	3.8 (2.9-4.7)	14	4.2 (2.6-5.8)
Benzodiazepines	3	2.3 (1.0-3.6)	4	1.2 (0.0-2.9)
Atypical antipsychotics	2	1.5 (0.7-2.3)	2	0.6 (0.0-1.4)
Miscellaneous anticonvulsants	1	0.8 (0.4-1.2)	4	1.2 (0.0-2.9)
Top Adverse Drug Reaction Symptoms				
Constipation	13	9.8 (4.8-14.8)	26	7.9 (5.0-10.8)
Dizziness	10	7.5 (3.7-11.3)	15	4.4 (2.5-6.3)

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Diarrhea	10	7.5 (3.4-11.6)	22	6.2 (3.7-8.7)
Rash	9	6.0 (2.0-10.0)	25	7.6 (4.7-10.5)
Hyponatremia	8	5.3 (1.5-9.1)	21	6.1 (3.5-8.7)
*95% confidence intervals (95%CI) adjusted for clustering of adverse drug event characteristics in patients with multiple events.				