Introduction:

Inappropriate polypharmacy is an emerging health issue that is associated with poor clinical outcomes, but potential for reversibility[1].Polypharmacy is commonly defined as exposure to five or more regular medications[1, 2]. There is an escalating trend of cumulative prescriptions, particularly for older patients who have tended to accumulate the number of, and classes of, medications over their lifespans that coincides with increasing diagnoses[1,2].Polypharmacy becomes problematic when the body's physiological reserve lacks the capacity to tolerate the potential adverse drug reactions and is often coupled with changing pharmacokinetic parameters as in most cases of frailty syndrome, and/or when the medications are no longer indicated or suitable for that person's goals of care or stage of life, particularly with end-stage conditions[2]. Problematic polypharmacy is associated with various adverse drug reactions and complications, ranging from falls, and delirium, to institutionalised care and mortality [2, 3]. From an acute hospital's perspective, polypharmacy has been associated with increased length of stay, recurrent emergency department presentation, and nosocomial complications[4, 5].

This document provides a guideline for identification of potentially inappropriate medications (PIMS), problematic polypharmacy, and a subsequent deprescribing strategy.
The guideline describes the following:
1. Identification of problematic polypharmacy and PIMS.
2. Targeting of specific medications with view of deprescribing when clinically appropriate. The guideline is limited to those medications where deprescribing is unambiguous and more context independent.

1. Identification of problematic polypharmacy:

a. Target patient groups:

- Aged 75 years and older with frailty.
- Five or more regular medications (polypharmacy).
- End-stage chronic conditions.
- Significant comorbidities (e.g. those with high Charlston Comorbidity Index scores).[6]
- Palliative stage or final year of life (may be estimated by the "Surprise Question")[7]. Discussion about goals of care and goals of life, may range from comfort-based care only, to active care for symptomatic control and quality of life rather than prolongation of life.

b. Review of current medications:

- Medication reconciliation to ensure a complete and accurate list is obtained.
- Review of current indication for each medication/class
- Matching whether current medication regimen reflects appropriate clinical indication and whether current indication is appropriate for stage of life and goals of care

2. Targeting of PIMS
For the propose of this guideline, the following classes of medications will be included with clear deprescribing criteria, with target population group as per previous page:

a. Cholesterol lowering agents (statin class, fibrates, ezetimibe, nicotinic acid)
b. Antiplatelets (aspirin, clopidogrel, dipyridamole)
c. Proton pump inhibitors
d. Bisphosphonates
e. Hypoglycaemic agents

a. Cholesterol lowering agents:
STOP statins in the following situations (no need for weaning):

- Primary prevention (i.e. no prior history of IHD, stroke or TIA, or PVD) in those aged 75

a. Cholesterol lowering agents:

STOP statins in the following situations (no need for weaning):

- Primary prevention (i.e. no prior history of IHD, stroke or TIA, or PVD) in those aged 75 years and older with frailty, or patients with life expectancy of less than 5 years.
- Secondary prevention and life expectancy of less than 5 years, or goals of care is centred on comfort-based or symptomatic care only, or those with frailty syndrome aged 75 years and older.
- Secondary prevention in those aged 75 years or older, and greater than five years exposure on statin with stable vascular disease.
- Adverse effect including myopathy and falls exceed potential clinical benefit.

STOP bezafibrate and/or ezetimibe (unless indicated for prevention of pancreatitis induced hypertriglyceridaemia.

Rationale

- The role of statins in primary prevention of cerebral and cardiac events, particularly for people aged ≥ 85 years, is unclear and may result in exposure to unnecessary harms[8, 9, 10]. This age group also has an increased risk of adverse effects from statins, particularly myopathy[8,9]. Muscular symptoms have been reported in 10% of patients within one month of high dose statin initiation. In the most severe cases, muscular pain confined patients to bed[11].
- The Numbers needed to treat (NNT) for statins in primary prevention of cardiac and cerebral events are reported in the order of 70 and 130 over five years[9].
- Lipid lowering therapy in secondary prevention is effective in reducing major vascular events in younger patients. Every 1mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) has been associated with a 23% reduction in vascular events in patients with a mean age of 62 years[12].
- Surrogate markers, such as LDL cholesterol (LDL-C), should however be interpreted with care in older people. Epidemiological data indicate that lowering LDL-C has a smaller impact on the relative risk of coronary heart disease as age increases[14]. Meta-analysis of statins in older patients, average age 75 years, have shown a NNT of 333 for every 1mmol/L reduction in LDL-C to prevent a major vascular event[10].
- The NNT for statin therapy in the secondary prevention of cerebral and cardiac events are reported to be between 20 and 40 for five years of treatment[9,14,15]. The PROSPER trial[13] randomised patients with cardiovascular (CV) disease or risk factors for CV disease with a mean age of 75 years to either pravastatin or placebo for an average follow up of 3.2 years. For patients with prior vascular disease, the primary end point of coronary death, MI or stroke occurred in 17.4% of the statin group and 21.7% of the placebo group. (NNT 23.2 over 3.2 years).
- Meta – analyses suggest that 80% of the lipid-lowering effects of statins occur at half the maximal statin dose [9,14]. Of note, the adverse effects to the statins are dose related[9]. A trial of more intensive statin therapy in those with a history of MI (80mg simvastatin versus 20mg daily) did not show a significant difference in the primary endpoint of major vascular events. (Major vascular events occurred in 24.5% of the intensive arm versus 25.7% in the 20mg arm. Risk ratio 0.94,95% CI: 0.88-1.01, p=0.10)[16].
- Fibrates primarily lower triglycerides and increase high density lipoprotein high density lipoprotein cholesterol. They have not however been reliably shown to reduce CV morbidity or mortality when prescribed as either monotherapy or in combination with other agents[17].
- Ezetimibe inhibits the absorption of dietary cholesterol in the small intestine resulting in reductions in LDL-C. Most current guidelines do not recommend ezetimibe for lipid-lowering for primary or secondary prevention[17].
- Nicotinic acid is no longer recommended as a lipid-lowering treatment, either as a monotherapy or in combination with a statin[17].

1. (Masnoon et al. What is polypharmacy? A systematic review of definitions. BMC Geriatrics 2017;17;230: 1-10)
2. Van Der Cammen et al. Drug cessation in complex older adults: time for action. Age and Ageing 2014; 43:20-25.
3. Shah et al. Polypharmacy, Adverse drug reactions and geriatric syndromes. Clin. Geriatr Med 2012; 28: 173-186.
4. ɔe T, et al. Polypharmacy as a risk factor for hospital admission among ambulance-

3. Shah et al. Polypharmacy, Adverse drug reactions and geriatric syndromes. Clin. Geriatr Med 2012; 28: 173-186.
4. ɔe T, et al. Polypharmacy as a risk factor for hospital admission among ambulance-transported old-old patients. *Acute Med Surg*. 2015;3(2):107-113.
5. Graziano O, et al. Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age and Ageing*; 2013; 42 (3): 284–291.
6. Available from URL: https://www.mdcalc.com/charlson-comorbidity-index-cci
7. hite N, et al. How accurate is the 'Surprise Question' at identifying patients at the end of life? A systematic review and meta-analysis. *BMC Med*. 2017;15(1):139.
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9. Consultant Pharmacy Services. A guide to deprescribing Statins CPS. Available from URL: http://www.consultantpharmacyservices.com.au/ Cited 13/05/2020
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13. Shepherd et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360: 1623-30.
14. Hilmer, S, et al. Statins in older adults. *Aust Prescr* 36.3; 2013: 79-82.
15. Schiattarella, Gabriele Giacomo, et al. "Statins and the elderly: recent evidence and current indications." *Aging Clin Exp Res* 24.3 Suppl (2012): 47-55.
16. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010; 37 (6):1658-69.
17. bpac nz Prescribing statins to reduce cardiovascular risk. bpac^{nz}, September 2017. Available from https://bpac.org.nz/2017/statins.aspx (Accessed August 2020)

b. Antiplatelets

STOP antiplatelets in the following situations (no need for weaning):

- Primary prevention (i.e. no prior history of IHD, stroke or TIA, or PVD) in those aged 75 years, with frailty.
- Adverse effects including gastro-intestinal (GI) bleeding, or the presence of anaemia exceed potential clinical benefit.
- Secondary prevention and life expectancy of less than 5 years, or goals of care is centred on comfort-based or symptomatic care only.
- Patients receiving dual antiplatelet agents should generally have one of the agents ceased within 3-12 months of the acute event. Where there is a high risk of bleeding (e.g. elderly, concomitant prescription of other GI bleed inducing agents), earlier cessation may be appropriate.

Rationale

- For patients that have a five-year CV risk ≥ 15% and are aged ≥ 70 years, the use of aspirin for primary prevention is not recommended due to an increased risk of major bleeding, without reducing the risk for cardiovascular events[18].
- Low dose aspirin treatment trials in healthy older adults, with no vascular history, have shown a rate of major haemorrhage of 8.6 events per 1000 patient years in the aspirin arm versus 6.2 events per 1000 patient years in the placebo arm after 4.7 years of follow up. The rate of CV events was recorded as 10.7 events per 1000 patient years in the aspirin arm versus 11.3 events per 1000 patient years in the placebo group[19].
- The use of aspirin versus placebo to reduce primary CV events, in those with a history of diabetes, was unable to show a statistical benefit in those over 60 years of age. (Primary event, first composite of a non-fatal MI, non-fatal ischaemic CVA/TIA or death from vascular

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- Of note, no available CV risk calculators cater for patients older than 75 years. Individual assessment of coexisting risk factors, patient prognosis and the potential impact of a cardiovascular event could assist in the determining the benefit of ongoing therapy[18].
- Low-dose aspirin has been shown to be effective in preventing one-fifth of atherothrombotic vascular complications (non-fatal MI, non-fatal stroke, or vascular death) in patients with previous MI, stroke, or transient cerebral ischemia [8, 18]. For secondary prevention, the absolute risk reduction (ARR) is 2-4% per year, NNT 25-50[18].
- The benefit of aspirin in secondary prevention is weighted against an increased risk of bleeding. Meta-analysis of antiplatelet therapy in high risk patients has recorded that 20% of major extracranial bleeds are fatal[21].
- Patients age 75 and older have been underrepresented in clinical trials of acute coronary syndrome and specific guidance for duration of dual antiplatelet therapy is unclear[18].
- The risk of major bleeding associated with dual antiplatelet therapy has been shown to be more than twice that of either agent prescribed alone[22].
- The American Heart Association guidelines for use after acute cardiac syndromes recommended dual antiplatelet therapy for 12 months in the absence of significant contraindications. The guideline also stipulates that "Management decisions with non–ST-elevation acute coronary syndrome should be patient centred, and consider patient preferences/goals, comorbidities, functional and cognitive status, and life expectancy"[23].

18. Consultant Pharmacy Services. A guide to deprescribing antiplatelet agents CPS. Available from URL: http://www.consultantpharmacyservices.com.au/ Cited 13/05/2020
19. McNeil et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. N Engl J Med 2018;3791509-18.
20. Bowman et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018; 379(16):1529 -39.
21. Antithrombotic Trialists' Collaboration Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71–86
22. Usman, et al. "Combination antiplatelet therapy for secondary stroke prevention: enhanced efficacy or double trouble?" *The American journal of cardiology* 103.8 (2009): 1107-1112.
23. *2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*

c. Proton pump inhibitors (PPIs)

STOP PPIs in the following situations (weaning may be required, please refer to rebound hypersecretion of gastric acid below):

- Gastro-oesophageal reflux disorders (GORD) that has been treated for 4-8 weeks and patients have no current symptoms.
- Peptic ulcer disease with known underlying case removed/treated (NSAIDs, H. *pylori)*.
- Prescription for gastro-protection due to other medications that have or can be discontinued (NSAIDs, dabigatran, oral bisphosphonates).
- Mild-to-moderate oesophagitis or reflux that can be managed with antacids.

Rationale

- PPIs are effective and generally well tolerated when used short-term for relieving upper gastrointestinal symptoms of GORD and healing oesophagitis [24,25, 26]. Approximately 85% of patients with erosive oesophagitis have complete healing at 8 weeks[26, 28].
- A few hypersecretory conditions may however require long term treatment with PPIs, sometimes at higher dose. These include severe oesophagitis, oesophageal stricture and/or scleroderma, prevention of relapse where eradication therapy for H. *pylori* has failed, Zollinger-Ellison syndrome and prophylaxis in patients with long term NSAIDs who are at high risk of ulceration[24,27].
- PPIs are widely used so adverse effects that occur less frequently may still be observed in

Zollinger-Ellison syndrome and prophylaxis in patients with long term NSAIDs who are at high risk of ulceration[24,27].

- PPIs are widely used so adverse effects that occur less frequently may still be observed in normal clinical practice[24]. Long-term PPI use has been associated with an increased risk of several adverse outcomes in longitudinal studies including the following;[24, 25, 26]:
  - **Due to reduced or modified absorption of nutrients:** Vitamin B12 deficiency, deduced calcium absorption with increased bone loss and increased fractures, decreased magnesium and iron absorption
  - **Due to altered PH of the gastric contents:** Increased enteric infections (including C. *difficile)* and increased risk of community and hospital acquired pneumonia.
  - **Idiosyncratic:** Acute interstitial nephritis and altered bioavailability/ metabolism of other medications

Rebound hypersecretion of gastric acid

- Stopping PPI treatment can cause rebound acid hypersecretion, such as indigestion leading to the transient appearance of symptoms[24].
- A 'step down' approach may be considered where withdrawing the PPI is appropriate. Stepping down involves gradually reducing the dose over time e.g. two to four weeks before stopping completely[25]. Several discontinuation strategies have been investigated[24]. If uncertain, please contact the pharmacy department for advice.
- After stopping, monitor for 4-12 weeks for re-emergence of symptoms, epigastric pain, dyspepsia, nausea. In non-verbal patients, look for regurgitation, weight loss, increased agitation or decreased appetite[27].

24.Consultant Pharmacy Services. A guide to deprescribing proton pump inhibitors CPS. Available from URL: http://www.consultantpharmacyservices.com.au/ Cited 13/05/2020A
25.bpac nz Stopping proton pump inhibitors in older people. bpacnz, January 2019. Available from: https://bpac.org.nz/2019/ppi.aspx (Accessed August 2020)
26. Khan et al. Medical treatments in the short- term management of reflux oesophagitis. Cochrane Database Syst Rev 2007:2.CD003244
27. Health quality and Safety Commission available from URL https://www.hqsc.govt.nz/assets/ARC/PR/Frailty_care_guides/Deprescribing-and-polypharmacy.pdf (accessed July2020).
28. Farrell, et al. Deprescribing proton pump inhibitors; evidence based clinical practice guideline. Can Fam Physician 2017;63: 35-64.

d. Bisphosphonates

STOP oral bisphosphonates in the following situations:

- Low risk of falls and immobility.
- No previous vertebral fractures and 5 years or more of treatment.
- Oral bisphosphates should not be used in patients with oesophageal disorders (achalasia, oesophageal stricture, barrettes oesophagus, oesophageal varices. They should also be avoided after certain types of bariatric surgery.
- Hypocalcaemia
- Renal impairment with CrCl < 30ml/min

Rationale:

- In patients who have a low risk of falls, there may no longer be ongoing benefit to fracture risk reduction. Indeed, if the reduced falls risk is due to prolonged immobility, even the requirement to sit upright to administer the oral bisphosphonates may be sufficient reason to reconsider the therapy.
- There is currently little evidence to guide prescribing decisions beyond five years of treatment with oral bisphosphates, including the relative benefits and risks of re-initiating bisphosphonates after a drug holiday, and no clinical trials have investigated use beyond 10 years.

Adverse effects can become problematic for some patients

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- Bisphosphates are contraindicated in patients with moderate to severe renal impairment e.g. CrCl <30-35ml/min
- Gastrointestinal irritation occurs in 20-30% of patients (i.e. diarrhoea and abdominal pain)
- Some patients develop more severe GI symptoms such as reflux, dysphagia, esophagitis, and oesophageal ulcers
- Intravenous infusions can cause flu-like symptoms in approximately 30% of patients after the first infusion (i.e. fever, myalgia, and arthralgia).
- Hypokalaemia, musculoskeletal pain, ocular side effects and atrial fibrillation

Less common adverse effects (risk increases with age)

- Atypical femoral fractures – For every 1000 patients treated with bisphosphonates for three years, 11 hip fractures are prevented, compared to approximately one case of atypical femoral fracture caused. A 2016 report from the American Society of Bone and Mineral Research concluded that although findings were variable, it is likely that a longer duration of use of bisphosphates Leads to a greater risk of atypical femoral fractures, with incidence increasing from 16 per year for every 100,000 to 113 per year for every 100,000 people treated with bisphosphates. One study combining national prescription and hospital data in Sweden reported that the risk of atypical femoral fracture declines by 70% per year after stopping **bisphosphonates**.

- Osteonecrosis of the jaw has been reported in patients taking bisphosphates; however, approximately 90% of cases have occurred in patients exposed to high doses intravenously used in cancer management.
- The NNT over three years to prevent one vertebral fracture is 14-20, and at least 91 to prevent one hip fracture.
- Meta-analyses suggest that alendronic acid, Risedronate and zoledronic acid are similarly effective for reducing the risk of fractures.
- Withdrawing treatment for a one to two year period within this four to five years of additional treatment is recommended to reduce the risk of atypical femoral fracture

e. Glycaemic Control

Recommendations:

- Glycaemic targets should reflect the stage of life, including remaining life expectancy, cognitive function, functional status, falls risk and vulnerability. Refer to Table 1 below. Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147 .

- Prescribing of hypoglycaemics should be tailored to decrease the risk of hypoglycaemia. Shorr R, et al. Incidence and risk factors for serious hypoglycaemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997; 157:1681-1686.
  Munshi et al. Frequent hypoglycemia among elderly patients with poor glycaemic control. Arch Intern Med. 2011;171(4):362-364.

- Prescribing should prevent/minimise the incidence of symptomatic hyperglycaemia. Schwartsburd PM. Catabolic and anabolic faces of insulin resistance and their disorders: a new insight into circadian control of metabolic disorders leading to diabetes. Future Sci OA. 2017 Jun 26;3(3): FSO201.

Patient characteristics/health status	Reasonable $HbA1_c$ goal	Fasting or pre-prandial glucose
Healthy	<58mmol/mol (7.5%)	5.0-7.2mmol/L
Complex/intermediate	<64mmol/mol (8.0%)	5.0-8.3mmol/L

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Complex/intermediate	<64mmol/mol (8.0%)	5.0-8.3mmol/L
Very complex/poor health	<69mmol/mol (8.5%)	5.6-10.0mmol/L

Rationale:

The following factors increases the risk of hypoglycaemia in older people:-

1. Being on greater than five medicines at any one time
2. Having recently been discharged from hospital in the last thirty days
3. Having poor cognitive function
4. Having low weight (ie:- BMI <25)
5. Having poor renal function

Hypoglycaemia in older people has been found to cause the following problems:-

1. Increased risk of falling
2. Increased risk of dementia
3. Increased risk of strokes
4. Increased risk of heart attacks
5. Increased risk of

Hypoglycaemia in the older adults is associated with the following complications:

- Polypharmacy (>5 meds) and inpatient admission higher risk of drug induced hypoglycaemia
- Higher risk of hypoglycaemia within 30 days of discharge from hospital.
- Associated with poor cognition, with cognitive impairment can increase risk of hypoglycaemia, AND hypoglycaemia can worsen cognition.
- Associated with falls and falls related complications and injuries.
- Poor renal function and low body weight are high risk of developing hypoglycaemia
- Hyperglycaemia does not exclude hypoglycaemia

- Older adults with frailty, those who are prescribed >5 medications and those who are frequently admitted to hospital, are at a higher risk of drug-induced hypoglycaemia.
  Shorr R, et al. Incidence and risk factors for serious hypoglycaemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997; 157:1681-1686.

- 53% of patients with a HbA1c target of (48 mmol/mol) 6.5% in the ADVANCE study experienced an episode of hypoglycaemia.
  The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. June 12, 2008. N Engl J Med 2008; 358:2560-2572.

- An increased risk of hypoglycaemia has been associated with dementia and impaired cognition.
  Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.
  Mattishent, et al. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. Diabetes, obesity, and metabolism. 2016;18(2):135-141.

- Hypoglycaemia is associated with an increased rate of falls and fall-related outcomes including fractures, head-injuries, long-term care placement and hospital admissions.
  Kachroo S, Kawabata H, Colilla S, Shi L, Zhao Y, Mukherjee J, Iloeje U, Fonseca V. Association between hypoglycemia and fall-related events in type 2 diabetes mellitus: analysis of a U.S. commercial database. J Manag Care Spec Pharm. 2015 Mar;21(3):243-53.

- Older adults (≥ 75 years of age), those with a BMI < 25kg/m^2 and patients with renal impairment are more likely to develop hypoglycaemia.

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  Miller Michael E, Bonds Denise E, Gerstein Hertzel C, Seaquist Elizabeth R, Bergenstal Richard M, Calles-Escandon Jorge et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study BMJ 2010; 340 :b5444

- Patients are more likely to develop hypoglycaemia within 30 days of discharge from hospital.
  Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997 Aug 11-25;157(15):1681-6.

- Hypoglycaemia episodes are common in older adults, even in a setting of poor glycaemic control. In those with an elevated HbA1c (≥8%), as many as 93% of patients have been shown to be unaware of hypoglycaemic events.
  Munshi MN, Segal AR, Suhl E, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. *Arch Intern Med*. 2011;171(4):362-364.