IM - REVIEW

Polypharmacy in older people: lessons from 10 years of experience with the REPOSI register

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Abstract

As a consequence of population aging, we have witnessed in internal medicine hospital wards a progressive shift from a population of in-patients relatively young and mainly affected by a single ailment to one of ever older and more and more complex patients with multiple chronic diseases, followed as out-patients by many different specialists with poor integration and inevitably treated with multiple medications. Polypharmacy (defined as the chronic intake of five or more drugs) is associated with increased risks of drug–drug interactions and related adverse effects, prescription and intake errors, poor compliance, re-hospitalization and mortality. With this background, the Italian Society of Internal Medicine chose to start in 2008 a prospective register called REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) in internal medicine and geriatric hospital wards. The country wide register is an ongoing observatory on multimorbidity and polypharmacy in the oldest old, with the goal to improve prescription appropriateness and, thus to avoid potentially inappropriate medications. The main findings of the register, that has accrued so far, 7005 older patients throughout a 10 year period, are summarized herewith, with special emphasis on the main patterns of poor prescription appropriateness and related risks of adverse events.

Keywords Multimorbidity · Polypharmacy · Inappropriate prescription · Deprescribing · Medication reconciliation

Introduction

Aging is a global issue, not only in high-income countries, but also in more vulnerable economies. According to WHO, older people are the age group in more rapid growth, and in the 2050s, two billion people (one in four) will be older than 60 years, and as many as 80% of them will live in low-income countries. Planetary aging is good news, owing to the progress of medicine, improved lifestyles and the availability of medications that have changed the course of many ailments. However, aging has a number of negative consequences, such as a proportional decrease of the working class of the countries where more and more people live longer. Furthermore, the gross domestic product of these countries is jeopardized by the burden exerted on welfare by senior citizens with multiple chronic diseases and related disabilities. Italy is one of the countries with higher life expectancy at birth. Within the year 2050, 24% of the population will be older than 65 years and 15% of them will be older than 80 years. Furthermore, the very low fertility rate (1.3 per woman in Italy) is causing a marked disproportion between older people and active citizens. This entails more and more difficulties in sustaining welfare systems, leading to higher out-of pocket costs for each citizen or their neglect of adequate health care. There are other formidable problems, including those related to the increase in the elderly of frailty, cognitive deficits and disability.

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Shifts in internal medicine wards

With this background, Italian internists did progressively realize that during the last 20–30 years of their practice there were dramatic changes in the type of patients acutely admitted to hospital wards. There has been a progressive shift from a population of adult in-patients usually affected by a single acute disease to one of ever older and more and more complex people with multiple chronic diseases, frequently attended before hospital admission by many different specialists, with poor integration of their care and the prescription of multiple medications. Beside taking 5 or more drugs (the most frequent definition of polypharmacy), these patients often need longer and longer hospital stays, not only for the complexity of their clinical conditions but also for the difficulties in planning their home discharge owing to the previous existence or novel onset of many functional and social problems aggravated by acute diseases and hospitalization. We also became aware that so many drugs, prescribed to multimorbid patients on the basis of the evidence stemming from the guidelines for each single disease, were causing new issues and problems.

Polypharmacy and its consequences

According to Marengoni et al. [1], in 2060 "oldest old" people will reach 75 million in Europe (10–15% of the whole continent) and will consume more and more drugs. In Italy, the Italian Medicines Agency (AIFA) reports that 1.5 million of the oldest people (75–85 years) are being prescribed 6 or more daily drugs, and that the number of people on polypharmacy is predicted to reach 6 million in 2050. Older people currently absorb nearly two-thirds of the total budget for drugs provided by the Italian Health Service. Polypharmacy is not only an issue for the increasing costs of medications: it is associated with increased rates of mortality and re-hospitalization, so that polypharmacy itself should be perceived as a disease, often with more serious consequences of the diseases these different drugs have been prescribed for. This is due to the many negative effects of polypharmacy [2, 3]: drug–drug interactions and the related adverse effects, prescription and intake errors by both physicians and patients, poor compliance with prescribed drugs, plus the use in the "oldest old" of drugs that are inappropriate when life expectancy is limited [4, 5].

The limitations of evidence-based medicine

Why is polypharmacy so frequent in the elderly? It is the consequence of the inappropriate fragmentation of their care between multiple specialists, and the application to these complex multimorbid patients of the guidelines stemming from disease-oriented medicine that in turn stems from the results of randomized clinical trials (RCTs) on single specific diseases [6]. The snag is that RCTs enroll patients very different from the elderly, i.e., younger, usually with only one disease and a low baseline risk of adverse reactions to drugs. Thus, the RCTs provide evidence on drug efficacy, but not on effectiveness in real life, because they investigate the typical disease, not the actual patients with their own complex disease patterns [6]. Regulatory agencies that license drugs are cognizant of this problem; the European Medicines Agency states that "regulators must ensure that the development and evaluation of drugs take into account global demographic changes, so that safe and effective drugs reach the actual patients who ultimately use them" [7]. Taking as an example a complex condition most frequent in the "oldest old" such as heart failure, most RCTs enroll patients who are younger and with no or fewer comorbidities than those seen on real-life hospital wards of internal medicine [8].

The rationale for REPOSI

With this background, we chose to tackle to the issue of multimorbidity and related polypharmacy in the Italian older adults by starting and coordinating in 2008 a prospective register called REPOSI, sponsored by the Italian Society of Internal Medicine together with the IRCCS Mario Negri Institute for Pharmacological Research and a large research and teaching hospital in Milan (IRCCS Ospedale Maggiore). The register is based upon a prospective cohort of older patients (at least 65 years of age) acutely admitted to 107 Italian hospital wards of Internal Medicine and Geriatrics. Figure 1 summarizes the setting of the study. At the time of writing, we have already collected data on 7005 patients, and at least one-third of them are older than 85 years, with a mean age of 80 years. Figure 2 shows the flowchart of the patients included so far. Table 1 shows the main characteristics of the actually enrolled patients, who are an accurate and actual picture of the ill people acutely admitted to Italian hospital wards of internal medicine and geriatrics. The main goal of this independent, investigator-driven register is to evaluate the pattern of drug prescription in hospital, in order to improve their appropriateness, and thereby help to avoid or at least reduce adverse reactions. Medication review and deprescribing during hospitalization have been emphasized, in order to avoid unnecessary dispensing and thereby attempting to prevent drug-related problems [9]. The decision to stop unnecessary medications is an important step towards drug optimization, so that deprescribing should be considered a positive, patient-centered intervention, which involves identifying an issue (the use of unnecessary drugs)
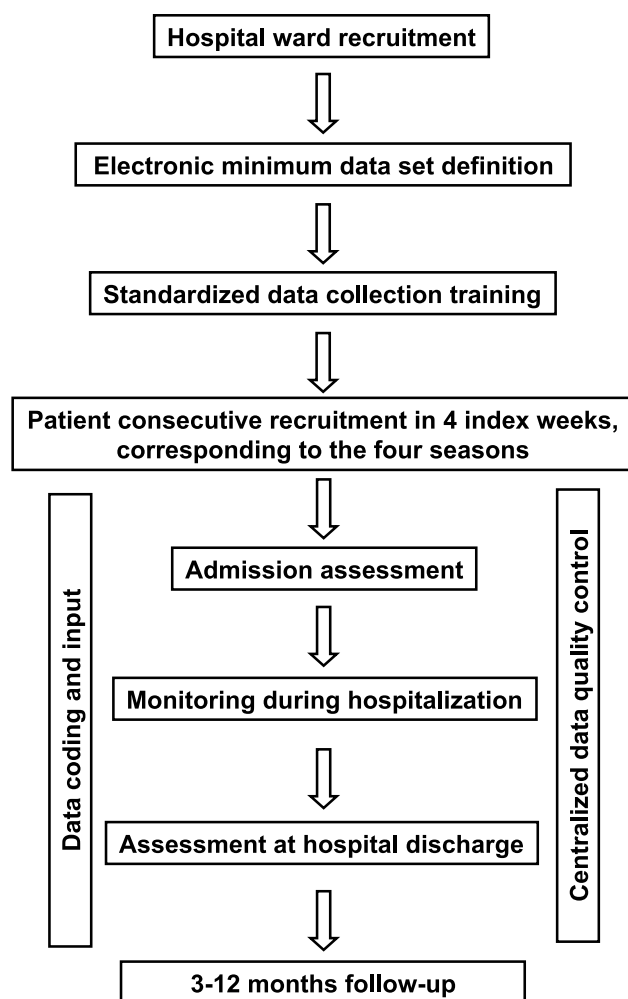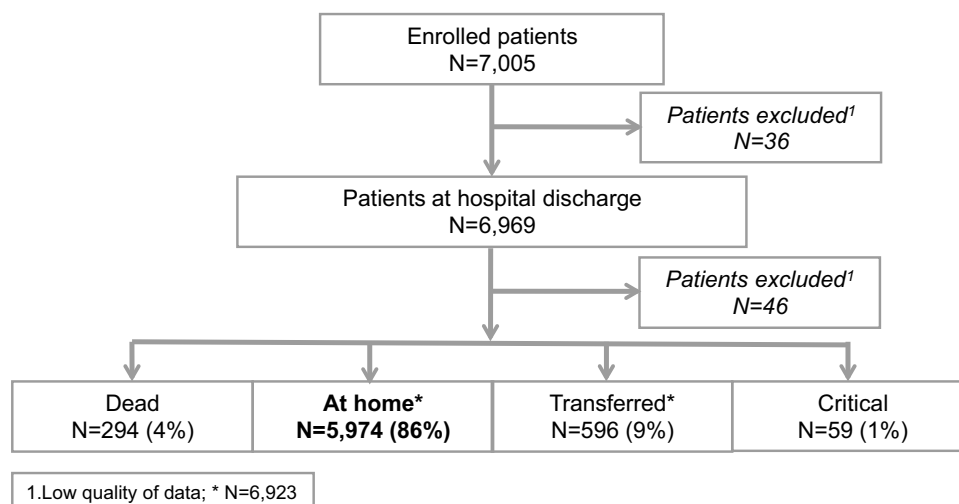
Fig. 1 Flow chart of REPOSI Register

and making a therapeutic decision (withdrawing them appropriately and with a close follow-up).

Main REPOSI findings

REPOSI has produced a number of reports stemming from the register (at the time of writing, 38 original articles, 5 letters to the Editor and 4 narrative reviews). Table 2 summarizes the main results. We confirm that in our Italian population of patients acutely admitted to internal medicine and geriatric hospital wards there is a high rate of polypharmacy (67% at the time of hospital discharge, more than at admission) [10]. The number of drugs is positively associated with a higher likelihood of re-hospitalization within the 3-month post-discharge follow-up [11]. Potential drug–drug interactions are frequent and associated with a more than twofold increased risk of mortality at 3 months after hospital discharge [12]. According to the 2003 and 2012 Beers criteria on drugs that should be avoided in older people, the prevalence of patients receiving at least one inappropriate medication is relatively high, at 20 and 24%, respectively [13]. Pertaining to the drugs most frequently inappropriately prescribed even according to the available guidelines, there are proton pump inhibitors [14], non-steroidal antinflammatory drugs (NSAIDs) [15], antibiotics [16], allopurinol [17], such antithrombotic drugs as anticoagulants [18–22] and antiplatelets [23], and, in general, all the classes of drugs active in the central nervous system (antipsychotics, antidepressants, opioids [24–27].) A definite increase in therapeutic duplicates of psychotropic drugs and drugs for peptic ulcer is also observed at hospital discharge, although duplication increases the risk of adverse drug events and costs [28]. Drugs with anticholinergic effects are associated with cognitive and functional impairment [29], and the recognition and management of delirium were rather inadequate in the

Fig. 2 Overall recruitment and hospital outcomes of REPOSI cohort

Table 1 Main socio-demographic and clinical characteristics of REPOSI patients during the period 2008—September 2017

Years of data collection	2008	2010	2012	2014	2015/2016	2016/2017
Number (N) of patients enrolled	1332	1380	1323	1212	800	958
Females, N (%)	721 (54.1)	696 (50.4)	672 (50.8)	622 (51.3)	442 (55.3)	470 (51.0)
Age (years), mean (SD)	79.3 (7.5)	79.0 (7.3)	79.3 (7.4)	79.1 (7.9)	80.4 (7.7)	80.1 (7.7)
Age class, N (%)						
65–74	409 (30.7)	430 (31.2)	403 (30.5)	365 (30.2)	192 (24.0)	254 (26.5)
75–84	607 (45.6)	650 (47.1)	583 (44.1)	529 (43.8)	350 (43.8)	405 (42.2)
> = 85	316 (23.7)	300 (21.7)	337 (25.5)	315 (26.0)	258 (32.1)	299 (31.2)
Need of caregivers, N (%)	–	772 (56.5)	689 (52.1)	595 (49.0)	386 (48.2)	496 (51.9)
Number of diagnoses at admission, mean (SD)	4.3 (2.3)	5.8 (2.8)	5.7 (2.8)	5.3 (2.9)	6.6 (3.2)	6.1 (2.8)
Number of patients at admission with 5 or more diagnoses, N (%)	571 (42.9)	884 (64.1)	839 (63.4)	640 (55.4)	576 (72.2)	661 (70.9)
Number of drugs at admission, mean (SD)	4.9 (2.8)	5.3 (2.8)	5.4 (3.1)	6.1 (3.1)	5.8 (3.1)	5.7 (3.1)
Number of patients at admission taking 5 or more drugs N (%)	689 (51.7)	805 (58.3)	778 (58.8)	760 (62.7)	516 (64.5)	607 (63.4)
CIRS-Severity index at admission, mean (SD)	–	1.6 (0.3)	1.7 (0.3)	1.7 (0.4)	1.7 (0.3)	1.7 (0.3)
CIRS-Comorbidity index at admission, mean (SD)	–	2.9 (1.7)	3.1 (1.9)	3.1 (2.0)	3.2 (2.0)	3.0 (1.9)
Barthel index at hospital stay, mean (SD)	–	76.8 (30.7)	72.6 (32.4)	70.8 (33.5)	67.5 (33.6)	70.9 (31.8)
Groups according to Barthel Index at hospital stay, N (%)						
Complete dependence (0–24)	–	155 (11.4)	169 (13.4)	176 (14.5)	130 (16.2)	121 (12.9)
Severe dependence (25–49)	–	111 (8.2)	126 (10.0)	104 (8.6)	64 (8.0)	93 (9.9)
Short Blessed test, mean (SD)	–	9.9 (8.2)	9.2 (7.8)	8.4 (7.9)	8.6 (8.1)	8.6 (7.6)
Short Blessed test, Severe (10–28), N (%)	–	637 (47.6)	541 (44.5)	406 (40.4)	276 (41.07)	311 (39.4)
Geriatric Depression Scale, mean (SD)	–	1.4 (1.2)	1.4 (1.2)	1.3 (1.2)	1.3 (1.3)	1.3 (1.3)
Dead, N (%)	66 (5.0)	50 (3.6)	42 (3.0)	68 (5.6)	36 (4.5)	32 (3.5)
Number of patients discharged, N (%)	1155 (86.7)	1159 (84.0)	1159 (87.6)	1053 (86.9)	681 (85.2)	778 (81.2)
Number of diagnosis at discharge, mean (SD)	5.9 (2.5)	6.5 (3.0)	6.3 (2.8)	5.9 (3.1)	7.0 (3.3)	7.1 (3.0)
Number of patients at discharge with 5 or more diagnosis, N (%)	796 (68.9)	857 (73.94)	834 (72.0)	637 (60.5)	525 (76.8)	626 (81.1)
Number of drugs at discharge mean (SD)	6.0 (2.9)	6.3 (2.8)	6.4 (3.1)	7.8 (5.5)	6.2 (3.3)	6.5 (3.3)
Number of patients at discharge taking 5 or more drugs N (%)	770 (66.7)	838 (72.3)	838 (72.3)	885 (84.0)	494 (71.0)	573 (73.3)
CIRS-Severity index at discharge, mean (SD)	–	1.7 (0.3)	1.7 (0.3)	1.7 (0.4)	1.7 (0.4)	1.7 (0.3)
CIRS-Cormobidity index at discharge, mean (SD)	–	3.0 (1.8)	3.2 (2.0)	3.2 (2.1)	3.2 (2.1)	3.2 (2.0)
Hospital stay days, mean (SD)	11.1 (8.5)	10.9 (8.2)	11.4 (8.5)	12.3 (10.5)	12.8 (17.2)	13.4 (17.3)

CIRS Cumulative Illness Rating Scale

internal medicine wards participating in the register [30]. Importantly, we recently observe that the 27 wards that had regularly participated in the different runs of REPOSI from its onset did improve the rate of polypharmacy compared with the 2010 run. In fact, considering each year of the study period, the proportion of patients prescribed at discharge with 0 to 1 drugs (very low drug use) with respect to those prescribed 2 or more increases from 2.7 to 9.2%, while patients exposed to 5 to 9 drugs decrease from 83.8% in 2010 to 76.8% in 2016 [31]. Furthermore, among hospitalized older patients, we are able to distinguish a gender dimorphism in the demographic and morbidity profiles of hospitalized elderly people [32, 33], different clusters of diseases [34–36] and frailty phenotypes (the healthiest, those with multimorbidity, the functionally independent women with osteoporosis and arthritis, and the functionally dependent "oldest old" patients with cognitive impairment), differently associated with adverse events [37], emphasizing once more the need for a personalized process of healthcare. Finally, we also observe that the increasing score of the Frailty Index (FI) (according to the model of the age-related accumulation of deficits) is significantly associated with in-hospital and overall mortality, also after adjustment for age and gender. The FI is a simple and useful tool that measures the frailty status of hospitalized older people, and that may thus facilitate their appropriate hospital management, by informing whether or not care should be adapted for the most vulnerable elders at discharge [38]. A full list of the REPOSI published articles has been added in the supplementary material.

Table 2 Summary of main results of REPOSI Register

Drug utilization
High frequency of polypharmacy (67% at discharge) [10]
A gender difference in overall medication pattern in the hospitalized elderly is found: hospitalization, while increasing the number of prescriptions, does not change drug distribution by gender [33]
The prevalence of patients with chronic pain prescribed with opioids is low at admission (4%) and increases only slightly at discharge (6%) [26]
The strongest association between clusters of diseases and polypharmacy is found for diabetes mellitus plus coronary heart disease plus cardiovascular disease, diabetes plus coronary heart disease, and heart failure plus atrial fibrillation [36]
From 2010 to 2016, there is an increasing number of patients who, on polypharmacy at hospital admission, decrease drug intake at hospital discharge [31]
Appropriateness of drug prescribing
Severe drug-drug interactions are frequent (24%) and associated with an increased risk of 3-month mortality (odds ratio: 2.62) [12]
The prevalence of patients receiving at least one potentially inappropriate medication is 20 and 24% according to the 2003 and 2012 versions of the Beers' criteria [13]
The prevalence of patients exposed to at least one therapeutic duplicate rises significantly from hospital admission (2.5%) to discharge (3.4%; $p = 0.003$) [28]
There is a high frequency (63%) of inappropriate prescription of proton pump inhibitors [14]
Among patients treated with antiplatelet therapy for primary prevention, 52% are inappropriately prescribed (mainly overprescribed, 74%), also with a high rate of inappropriate underprescription in the context of secondary prevention (30%) [18]
Appropriate antithrombotic prophylaxis has a prevalence of less than 50% in patients with atrial fibrillation, with an underuse of vitamin K antagonists agents independent of the level of cardio-embolic risk [19]
Non-compliance to guidelines is highly prevalent among elderly patients with atrial fibrillation, despite guideline-compliant treatment being independently associated with lower risk of all-cause and cardiovascular deaths [20]
Among patients treated with allopurinol more than 90% are treated inappropriately at admission and at discharge [17]
Despite their risk, QT-prolonging drugs are widely prescribed to hospitalized older persons [44]
Prognostic measures
The number of drugs is significantly associated with the likelihood of readmission at 3 months [11]
The documentation of delirium is poor (2.9%) on medical wards of Italian acute hospitals [30]
Patients with cognitive impairment are more likely to die during hospitalization with a severity-dependent association [25]
Drugs with anticholinergic properties are associated with worse cognitive and functional performance [29]
Severely reduced eGFR at admission is associated with in-hospital mortality (OR 3.00; $p = 0.02$), and a decreased eGFR at hospital discharge is associated with an increased risk (OR 2.60 $p = 0.08$) to die within 3 months after discharge [45]
No difference in predictive power between different e-GFR equations is found [46]
Mild anemia predicts hospital readmission in older in-patients, while the three-month mortality risk increases proportionally with anemia severity [47]
Elderly hospitalized patients with pneumonia and clinically significant disability have a higher mortality risk, while diabetes does not represent an important determinant of short and long-term outcome [48]
Bedridden status, severely reduced kidney function, recent hospital admissions, severe dementia and hypoalbuminemia are associated with higher risk of three-month mortality in non-oncologic patients after discharge [49]
The increasing score of Frailty Index (according to the age-related accumulation of deficit model) is predictive of both in-hospital (OR 1.61, 95%CI 1.38–1.87) and overall (HR 1.46, 95%CI 1.32–1.62) mortality, also after adjustment for age and gender [38]

Lessons from REPOSI [39]

First of all, REPOSI provides a collaborative clinical network (involving 107 internal medicine and geriatric hospital wards) for more than 300 young internists, who have the opportunity to be associated to an independent, real-life research project. They also have the possibility to learn directly from their clinical practice the appropriate use of drugs, the complexity of hospitalized older adults, and the importance of evaluating such domains as cognitive and functional status, mood disorders and the burden of polypharmacy, perhaps not previously considered by them to be so cogent. The registry also taught us that Italian hospital internists not only fail to optimally handle the multiple medications prescribed to their older patients, but also fail to improve during the hospital stay prescription patterns through medication reconciliation, medication review and deprescribing, and that these strategies are still far from their usual medicine practice. We also became aware that there is a need for a closer alliance between internists and geriatricians in the management of the oldest patients, and that the internists must become more proficient with the routine use of the tools of the comprehensive geriatric assessment [40]. This also entails the promotion and implementation of

a more interdisciplinary team approach to the hospitalized "oldest old," including clinical pharmacologists, hospital pharmacists, nurses and involving more than now patients, their relatives, caregivers and family doctors. There is more and more evidence for the crucial role played by the hospital pharmacist to support clinicians for medication reconciliation and review at hospital admission and discharge [41].

For each prescribed drug, more careful consideration should be given to the number of drugs taken, medication compliance, priorities and life expectancy of each patient, the time to benefit of each treatment, and the goals of care and treatment targets should be more accurately considered for a more rational prescribing. Patients may be more willing to stop unnecessary medications than their physicians believe [42]. Emphasizing the positive aspects of stopping medicines, reducing the burden of daily pills, improving compliance, and reducing the risk of drug–drug interactions and the associated adverse reactions are an approach that internists should pursue and emphasize in conversations with patients and relatives during the hospital stay and at discharge, involving in these choices the family doctors [43].

The future of REPOSI

There is a need for more research tailored to the peculiar features and needs of the multimorbid older patients on polypharmacy. For instance, RCT should be based on outcomes centered on the features and needs of people with a limited life expectancy (for instance, cognitive and physical function, emotional well-being and social connectivity) rather than on more traditional outcomes such as mortality, re-hospitalization and institutionalization. Because we are using multiple drugs that were originally evaluated and licensed in the frame of RCT of single drugs for single ailments, it is imperative to develop designs of new pragmatic trials, involving patients randomized to drug combinations chosen more rationally than hitherto, for instance in relation to disease clusters [34, 35]. Other research approaches in this population are to implement new designs of drug studies, such as network analysis, N-of-1 trials, narrative medicine and systems medicine.

Conclusions

We envisage REPOSI as a permanent observatory on multimorbidity and polypharmacy in the elderly, with the main goal being to improve prescription appropriateness and, thus, to avoid potentially inappropriate medications. This goal should be pursued by means of medication reconciliation, with regular reviews of the list of drugs and deprescribing those that are useless, dangerous or inappropriate when the life expectancy of the oldest patients is considered. The

huge available database of REPOSI is a still poorly explored source of information. We emphasize that the database is being made available and shared with those who are contributing to data collection, and are willing to test their own scientific projects, provided these are compatible and feasible with the available limited dataset. Finally, we point out that REPOSI is a rather unique endeavor, but with the limitation of depicting the situation of one European country only. We believe that similar registries should be considered in the frame of Internal Medicine settings in other countries, with the obvious advantage of accruing real-life data on the growing population of older patients.

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Compliance with ethical standards

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